THE CANADIAN MEDICAL ASSOCIATION

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

AUGUST 1, 1959 • VOL. 81, NO. 3

# CLINICAL CONNOTATIONS OF THE EXPERIMENTAL HYPERTENSIONS*

A. C. CORCORAN, M.D.,†
*Cleveland, Ohio*

To HONOUR the memory of a distinguished colleague is consonant with the aim of this lectureship. The present lecture is therefore dedicated to Dr. Eduardo Braun-Menéndez of Buenos Aires, Argentina, whose enduring contributions to the study of hypertension were cut short by his untimely death in the crash of an aeroplane in January 1959.

Osler believed that "in the records of no other profession is there to be found so large a number of men who have combined intellectual preeminence with nobility of character", and Dr. Braun-Menéndez's career exemplifies this. We are so accustomed to praise those who overcome odds of person or circumstance that we neglect the greater steadfastness of those who, like him, transcend the gifts of an attractive, warm personality, keen intelligence, broad cultural and scientific background, friends, family, and position. These are the truly dedicated. Few, like him, have conducted and oriented studies in a laboratory which, during political repression, he in part personally maintained as a centre of free science for his compatriots, for other Latin Americans, and for investigators from distant lands. Akin to Horace's "man of intact and blameless life", he fulfilled Thomas Fuller's directive that states it as the duty of a man "to better his heritage, and what his father found glass and made crystal . . . the son to find crystal and make pearl". His career is a further reminder of the "unbroken continuity", "remarkable solidarity", "progressive character", and "singular benevolence" that Osler considered the enduring characteristics of our profession, without regard to time, nation or place. To him then, homage. May he go with God!

Dr. Eduardo Braun-Menéndez

During the past 50 to 60 years hypertension has become an increasingly important cause of death and disability. Hypertension and arteriosclerosis together account for nine-tenths of present cardiovascular deaths; hypertension, alone or complicated by arteriosclerosis, accounts for about half of these. These millions of deaths only temporarily complicate lives of most who survive. But life also goes on for the incapacitated. Hence the bills of mortality do not begin to express the ravages and distress created by premature and prolonged disability, dependence and inactivity. The problem therefore has inestimably profound psychological, social and economic implications that affect us all as individuals and as members of the body politic.

## DEFINITION

Unfortunately, no definition of hypertension yet proposed is wholly inclusive or satisfactory. Most of them depend on more or less arbitrary enumerations of limits of normal arterial pressure; some beg the question by requiring the demonstration of associated vascular disease. Two recent, relatively

*Simmons-McBride Lecture, Faculty of Medicine, University of British Columbia, Vancouver, B.C., April 9, 1959. Presented April 13, 1959, to the Oregon Heart Association, Portland, Oregon.

†From the Division of Research, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio. Present address: St. Vincent Charity Hospital, Cleveland 15, Ohio.

Canad. M. A. J.
Aug. 1, 1959, vol. 81

liberal, numerical interpretations have been proposed by Master and his associates[1] and by Pickering.[2] Both arrive at roughly similar results from different statistical approaches, by making similar allowances for increased pressure with increased age. They are satisfactory within the framework of the British and American populations considered. However, populations have been described in which arterial pressure is stable throughout adult life. Further, life insurance tables[3] indicate that, in terms of excess mortality, the limits of normal may be lower than we think.

Any numerical solution of this problem is complicated by the normally fluctuant character of arterial pressure, the fallibility of measurement, racial differences and a whole series of factors that epidemiologists are just beginning to take into account.[4] Still, ever since Bright's tentative association of a hard pulse with a high pressure, the concept has spread that there is a point at which arterial pressure is persistently, if variably, abnormally high and that this state is associated with a course through diverse aspects of vascular injury lumped together as hypertensive vascular disease.[5] This, a description, has to serve as a definition until better criteria become available. Hence, in the majority of patients, physicians deal descriptively, in terms of a level of arterial pressure, the presence or absence of signs of hypertensive vascular disease and, if these are present, their site, relative severity, and static, slowly, or rapidly progressive character. Arbitrary numerical summaries of such estimates serve usefully in comparing groups of patients with one another or the present with the former status of the same patient group.[6]

A small proportion of patients present with hypertensions that can be etiologically defined as well as clinically described. These constitute the secondary hypertensions, experiments of Nature that, interpreted, cast light on the nature of the more common primary, or essential, hypertension. Further, during the past 25 years, experimental models of the secondary hypertensions have been elicited in animals. The study of these has clarified many aspects of the corresponding clinical syndromes and bears on the problem as a whole. The aim of this lecture is to develop the clinical implications and perspectives arising from aspects of the accumulated experimental data.

The secondary hypertensions are grouped as of neurogenic, endocrine, vascular, or renal origin. Each etiological category embodies correspondences between experimental models and clinical syndromes. As they pass in review, it will be evident that each is much less discrete than its name indicates. Prolonged disturbance of one pressor mechanism tends to upset the function of others. These secondary mechanisms may cause a hypertension to alter its character and even to become self-perpetuating after the primary cause is inoperative or has been removed.

## NEUROGENIC

Classical experimental neurogenic hypertension was first elicited by section of the sinoaortic buffer nerves in 1929.[7] This provokes a state of greatly increased vasomotor tone. Thoracic sympathectomy quiets the associated tachycardia; effects of renal denervation are equivocal but total sympathectomy abolishes the hypertension. The process seems to depend on a persistent vasomotor discharge with unmodulated liberation of norepinephrine at endpoints of vasomotor nerves; in some respects, as in shrinkage of plasma volume, it corresponds with the effect of infusions of pressor adrenergic amines. Clinical counterparts seem to occur, as in bouts of porphyria, lead encephalopathy, and some epidemics of poliomyelitis, but are incompletely characterized.

Beginning with the Cushing experiment, in which a sudden increase in intracranial pressure provokes an increase in arterial pressure, a large number of stimulating and destructive procedures affecting the central nervous system have been shown to evoke hypertension that is more or less prolonged. One of the more definite of these is cerebral ischæmia in rabbits or in dogs subjected to stimulation of the area of the third ventricle. Many reports are less definite or involve procedures that, from their nature, are of brief duration and may or may not be relevant to the problem of persistent hypertension.

Lay intuition cannot be disregarded; it commonly associates or even equates psychological with arterial tension. Most laymen are surprised to discover hypertension in some impassive, contented acquaintance or, with even less psychological validity, in a group such as the American or West Indian Negro,[8, 9] considered to be less responsive to their troubles than white people are. The basis of this lay judgment is suspect. Still, a great effort has gone into attempts at definition of a hypertensive personality pattern in hypertensive and prehypertensive states[10] and into demonstrations of causal associations between psychic trauma and hypertensive disease. The results are no more than suggestive, except for the common, well-documented[11] experience that psychic strain may intensify pre-existing hypertensive states or tendencies. As Pickering[2] states, "There is nothing inherently improbable in the idea," but he adds, "there is nothing conclusive about the evidence", when impartially reviewed. The Western literature has few relevant animal experiments, except those demonstrating increased arterial pressure in rats of selected strains exposed to prolonged, severe auditory stimulation.[12] However, a recent review[13] of Russian research on hypertension demonstrates a considerable mass of observations bearing on neurogenic aspects of experimental and clinical hypertension, much of it with a Pavlovian orientation, and some of it uncritical. The reviewers believe this accumulation is "a showcase exhibit of the need of integration of scientific information

on a world-wide basis", and contrast it with a recent concept of mechanisms in hypertension[14] which, for lack of available reliable data, neglected a statement on the role of the central nervous system. This is an aspect of pathogenesis that requires "very careful and laborious work"[2] and constant awareness of the tendency of preconceptions to persist as misconceptions.

The antihypertensive effect of reserpine, sometimes demonstrable in patients with severe,[15] as well as in those with mild, hypertensive disease, has been taken by some as indirect evidence of psychogenesis of hypertension. This drug, in sufficient dosage, mobilizes and depletes cerebral serotonin and other amines, alters function of the reticularis, diminishes vasomotor outflow, and may have profound psychic effects, salutary in mental disease, but sometimes distressing in those it unduly depresses. However, an accumulating body of evidence[16] indicates that the smaller doses used in hypertension may have sympatholytic vasodilator effects by peripheral norepinephrine dispersal which contribute to, if they do not wholly explain, its effectiveness. This *ex post facto* argument, like others relating to central disturbances of the genesis of hypertension, is inconclusive at best. The sporadic and unpredictable beneficial effects of lumbodorsal sympathectomy—surveyed from Smithwick's[17] series some years ago—or the more reproducible antihypertensive properties of ganglioplegic drugs[18] even more obviously fail to relate the nervous system to the genesis of hypertension, since these procedures merely impair one set of mechanisms that admittedly maintains normal as well as abnormal arterial pressure.

The primary modulation of arterial pressure is exerted through the baroceptor reflexes. Abolition of these in the dog leads to acute and, after a lag, persistent arterial hypertension. Volhard suggested that impaired baroceptor function might be the cause of hypertension. While available tests indicate normal baroceptor function in hypertension, albeit at a high level, Pickering[2] has asked if, in hypertension, these reflexes might be set at a new and higher level, which they would sustain just as they sustain pressure at lower levels in normal subjects. This does indeed occur in dogs with chronic renal hypertension. Stimulation of the afferent side of the baroceptor arc begins only at high levels of carotid sinus pressure, although responses are qualitatively normal within this range.[19] The result is that this system tends to maintain, by neural means, a hypertension which was primarily renal and humoral. Assuming, as seems likely, that this resetting can occur in hypertension of other origin and in other species, this can be visualized as a most significant mechanism in the self-perpetuation of hypertensive states. It is also a basic example of the tendency of hypertensive mechanisms to overlap systems and etiologies; it suggests that any persistent hypertensive state will become, in some measure, neurogenic.

### ENDOCRINE

Biologically, the endocrine messengers, the hormones, are primitive, sluggish, sustained equivalents of the refined, direct, highly specialized, and direct neural mechanisms of response to environmental change. Consequently, at their more archaic levels, neural mechanisms are indistinguishably or even demonstrably endocrine in their mediation. Hence, neural mechanisms overlap the endocrine and such a problem as psychological stress involves most levels of neural and many aspects of endocrine function.

The classic experiment is Selye's[20] induction of hypertension, nephrosclerosis and hypertensive vascular lesions[21] in uninephrectomized rats given desoxycorticosterone and salt. This has been abundantly confirmed and extended. However, his thought-provoking hypothesis of hypertension as a disease of adaptation[22] has not been widely accepted, because the problem transcends both the explanation and the available facts. But Professor Selye's predictions should never be undervalued; in accordance with them, differences have been established between the hypertensions caused by glucocorticoids and mineralo-corticoids, a naturally occurring, hypertension-producing[23] corticosteroid, aldosterone, has been isolated, and the corresponding clinical syndrome characterized[24, 25] in part by the concurrence with hypertension of signs of potassium deficit, somatic and renal. Interest in the adrenal origins of hypertension has been particularly stimulated by Skelton's[26] eliciting a salt-dependent hypertension during adrenal regeneration in young rats. The mechanism of this hypertension is unexplained; descriptively, it occurs concomitantly or as a sequel to cortical hypofunction, in which no other presently characterizable hormonal abnormality has been demonstrated.[27] Clinically, Cushing's syndrome demonstrates hypertension and nephrosclerosis with glucocorticoid excess, the hypertension sometimes persisting after adrenalectomy. Further, equivocal evidences of disturbed adrenal function and morphology occur in patients with hypertension.[28-30] Some have conducted therapeutic trials of total or subtotal adrenalectomy, the latter usually associated with subdiaphragmatic sympathectomy. Our clinical experience with adrenalectomy in severe hypertension has been entirely unrewarding: the logic of subtotal adrenalectomy in the light of adrenal regeneration seems perverse. However, available evidence indicates that this operation has not elicited a clinical adrenal-regeneration hypertension and that, in fact, possibly because of the associated sympathectomy, it is often helpful.[31]

Friedman[32] and Prado,[33] former associates of Selye and now in Vancouver and Brazil respectively, have independently described a post-desoxycorticosterone self-sustained hypertension. This was characterized by Selye as "metacorticoid hypertension". The topic has recently been reviewed.[34] It has particular interest in this dis-

Canad. M. A. J.
Aug. 1, 1959, vol. 81

cussion as another example of the tendency of a hypertension to persist after removal of its cause.

Hypertension-provoking properties of anterior pituitary factors other than the syndrome evoked by ACTH are attributable largely to growth hormone-supposititiously acting on a mineralocorticoid such as aldosterone—which might involve the pineal[35]—and should result in a more frequent association of hypertension with acromegaly than is demonstrable.[36] In brief, anterior pituitary, and in most instances, adrenal and thyroid[37] factors also, seem to be secondary, conditioning or permissive and not primary agents in human hypertension. Hence hypophysectomy and adrenalectomy may profoundly modify arterial pressure but they are far from being recommendable therapeutic procedures.

The posterior hypophysis exemplifies the narrow boundary between neural and endocrine functions; nuclei of its trophic nerves connect widely with midbrain centres and one of its secretions is a polypeptide neurohumour that regulates renal and extrarenal water exchange, may be pressor or depressor, and that participates in a neurohypophyseal axis concerned with equilibria of the sodium-transfer systems that have to do with tone and contraction of vascular smooth muscle.[38]

Hypertension due to functioning phæochrome tumours must be mentioned under the heading of the endocrine hypertensions, if only for completeness. This is an unusual, but not a rare cause of clinical hypertension. A high index of suspicion facilitates its recognition; a variety of test procedures confirm the diagnosis. The most direct is demonstration of excess catechol amines in plasma or urine. The chemical procedures are tedious, unless in routine use, so that expedients such as approximate bio-assay or observations of the effects of piperoxan on pressure and urine flow[39] may serve instead.

Two further aspects of endocrine function require particular mention. One is another instance of the interplay of systems. Injections of renin or experimental renal hypertensions involving secretion of renin stimulate the zona glomerulosa of the adrenal to hypertrophy; thus, a possible mineralocorticoid hypersecretion tends to counter the natriuretic effect of renin, but adds also to hypertension. A concept of this renal-adrenal interplay[40] proposed by Masson in 1951, has been extended by others[41, 42] and indicates still another self-perpetuating pathway of hypertension.

The second is that endocrine hypertension in the rat, except that caused by the glucocorticoids, is salt-dependent to a degree that suggests salt excess as primary mechanism of these hypertensive states, as in the syndrome produced in rats by severe salt excess alone[43] and its possible equivalent in salt-eating hypertensive American men.[44] Indeed, at the tissue level, cellular transfer mechanisms involving the sodium ion are concerned in responses to vasoactive agents[45] and may serve as the final common pathway for the actions of pressor amines, angiotensin, Pitressin, and some of the steroids.

### VASCULAR

The intervention of the sodium ion in the reactions of vascular muscle bridges into the next type of secondary hypertension. This is customarily thought of in terms of mechanical factors, as in coarctation of the aorta and in the systolic hypertension consequent on arteriosclerosis.[5] The repairability of coarctation makes it more than ever diagnostically important. Arteriosclerotic hypertension, due to loss of aortic and large vessel elasticity, on the other hand, is common and benign. Failure to differentiate between this labile systolic and persistent diastolic hypertension results in common, iatrogenic anxiety among our senior citizens and concern to their relatives, many of whom these good souls, particularly the old ladies, ultimately outlive.

But ultimately, vascular aspects of hypertension involve resolute analysis of such problems as vascular responsiveness,[46] the state of the smooth muscle, and its ionic balance. Disturbances at this level, as by the segregation of sodium water and electrolytes in hypertensive vessels,[47] may be crucial to the whole problem. At present, however, the evidence has not crystallized and clinical implications of sodium-depleting regimens and drugs are obscured by concurrent changes in blood volume and dynamics.

### RENAL

This, the last category of the secondary hypertensions, was first visualized by Richard Bright. He considered that the concurrence of nonvalvular heart disease with left ventricular hypertrophy with proteinuria and "morbid appearances of the kidneys" could be attributable to "some altered quality of the blood", that "so affects the minute and capillary circulation, as to render greater action necessary to drive the blood through the distant subdivisions of the vascular system".[48] His successors and interpreters, many of them also at Guy's Hospital—which has just observed the 100th anniversary of his death[49]—separated those cases in which heart disease was associated with generalized vascular rather than primary renal lesions. Their clinical and experimental studies amply associated the kidney with hypertensive disease but none as definitely, or with as profound, lasting and significant an impact as Goldblatt's observations in 1933 and 1934.[50]

The humoral mechanism of renal hypertension is the renal pressor system. This, as now defined, begins with renin, a catheptic enzyme associated with the juxtaglomerular apparatus,[42] released into the plasma as a result of impaired renal circulation. In plasma it acts on a specific group of a specific alpha-2-globulin, renin substrate[51] (angiotensinogen

or hypertensinogen), to split off a vasoinactive, 10-amino acid polypeptide, angiotensin I: another equally specific plasma enzyme — "converting enzyme"[52] — splits off two amino acids from angiotensin I to yield these and angiotensin II, a highly vasoactive, 8-amino acid polypeptide, formerly characterized[53] as angiotonin or hypertensin. Proteolytic enzymes of many tissues, including kidney, fragment angiotensin II into inactive residues; these enzymes do not seem to be specific but, for convenience, without prejudice to their heterogeneity, their activity can be characterized as that of "angiotensinase".

The reflective may be interested to know that the formulation just stated required more than half a century. It began in 1898 with Tigerstedt and Bergman's characterization of renin, came under active rather than desultory study in the late 1930's and reached what seemed to be an impasse in the simultaneous, independent characterization of angiotonin or hypertensin by Page and Helmer[54] in Indianapolis and by Braun-Menéndez and his associates[55] in Buenos Aires. Technical problems impeded hope for chemical and specific therapeutic accomplishment. The course of these studies has been reviewed at length by Dr. Braun-Menéndez and his associates.[56] Subsequently, development of paper chromatography and of methods for sequential analysis of peptide chains enabled definitive characterization of the angiotensins, again independently and simultaneously in two Cleveland[57, 58] laboratories and one London[59] laboratory. Thus do events wait on interest, effort and ability and these in turn upon the techniques and concepts of basic research.

Wakerlin[60] in particular, meanwhile, established the link between the renal pressor system and chronic experimental hypertension. With this and the chemistry secure, the long-anticipated specific chemotherapy of renal hypertension may be developed.

Effective and specific treatment of renal hypertension is now very largely a matter of accurate and early diagnosis. Renal malformations,[61] glomerulonephritis and degenerative changes contribute their share. The association of pyelonephritis with malignant hypertension was classically described by Weiss, Parker and Robb[62] and by Kimmelstiel and Wilson[63] more than 25 years ago but continues to be underestimated. This is in spite of the fact that data from routine autopsies in Copenhagen[64] and Prague[65] demonstrate that pyelonephritis is common, frequently unrecognized and frequently complicated by hypertension which, in about 15% of cases, is the proximate cause of death. Among the renal hypertensions, that due to pyelonephritis is peculiarly amenable to early diagnosis, prompt, adequate and, best of all, prophylactic treatment. The tendency to neglect this is exemplified by its omission from an otherwise inclusive, recent survey of preventive cardiology.[66]

The presumptive cause of hypertension in pyelonephritis is obliteration and destruction of medium-sized renal arteries,[67] while nephrosclerotic occlusion of smaller vessels contributes a renal component to hypertensions of extrarenal origin.

Curiously, in view of the Goldblatt clamp, occlusive disease of large renal vessels has been overlooked until fairly recently, having been first overestimated and then underestimated as a cause of hypertension. As so often happens, the defect was technical; until the development of innocuous techniques of renal angiography, *in vivo* diagnoses of these lesions were impractical. Thus, no cases were recognized at the Cleveland Clinic in the period 1945 to 1950, six were described in the period 1950 to 1954; and with increased use of this technique, 30 were demonstrated in 1955 and 1956 and 48 in 1957 and 1958.

A dramatic early instance of this condition occurred in a boy of 14 years who had a history of flank pain, extrarenal signs of malignant hypertension and a fatal cerebral hæmorrhage, and was found to have coarctation of the abdominal aorta with bilateral orificial stenosis of the renal arteries, and completely normal renal vascular and parenchymal structure.[68] A similar, less severe instance of orificial isthmic intimal fibroplasia was relieved by bilateral renal arterial homografts[69] and others have been reported,[70] so that this seems to constitute a syndrome of adolescent hypertension.

Much more common, however, are patients with atherosclerotic occlusions of renal arteries, unilateral or bilateral, and in main arteries or branches, with and without renal infarction, complicated in some by pyelonephritis.[71] A survey has established the situations that suggest the presence of renal arterial disease.[72] These are inequalities of renal size or excretory function, observed during urography or by means of radioisotope renograms[73] particularly in the absence of a family history; hypertension of recent onset and rapid progression, especially in patients less than 35 or more than 60 years of age; and the association of hypertension with flank pain.

The evaluation of such patients begins with simultaneous tests of the separate renal functions. Decreased filtration rate consequent on partial occlusion of a main renal artery considerably diminishes urine flow and sodium concentration on the affected side. Demonstration, during water diuresis, of such disparate function has gained some acceptance as diagnostic of unilateral renal arterial disease.[74] This is true, but as suggested above, the lesions and their sequelæ are commonly more complex. Both main renal arteries may be affected, so that function is diminished bilaterally and more on the more affected side, but the urine flow and sodium concentration give no indication that the lesions are bilateral. A lesion may obstruct a major renal arterial branch, diminishing renal mass—or the same may result from pyelonephritis;

Canad. M. A. J.
Aug. 1, 1959, vol. 81

experimentally the residual part of the kidney on that side may more than compensate in terms of urine flow and sodium output;[75] chemically, urine from this side may closely resemble that from the intact kidney. Lastly, concurrence of main arterial with branch lesions or of arterial lesions with parenchymal disease may greatly distort the relative composition of the urine. Thus, theoretical and practical considerations establish the evaluative worth of tests of separated renal functions under conditions that stabilize fluid and electrolyte outputs but show that these tests are not diagnostic in themselves;[76] a simpler expedient, the radionephrogram, provides similar, less detailed and specific information. Since indirect procedures, however elegant, cannot establish a specific anatomical diagnosis, renal angiography is a diagnostic *sine qua non* in selected cases.

Recognition of these lesions has led to surgical relief of the hypertension in an increasing number and proportion of cases; the procedures used include resection and anastomosis, endarterectomy or grafting in the lesions of main renal arteries, segmental or partial nephrectomy for branch lesions and, when technical limitations forestall conservative measures, uninephrectomy.[77]

An aspect of experimental renal hypertension that may carry over in human clinical syndromes of glomerular injury, such as toxæmia of pregnancy and systemic lupus erythematosus, has been simulated in rats, pretreated with desoxycorticosterone, other active steroids, or growth hormone or subjected to adrenal enucleation[37] and then given renin. In these, acute diffuse vascular lesions are associated with the formation of colloid-looking thrombi in glomerular capillaries. Enhanced pressor responsiveness to renin probably accounts for some of the lesions, since these are prevented by treatment with hydralazine; still, this may not be a complete explanation of this interesting phenomenon, the lesions of which in some respects resemble those of the accelerated Shwartzman reaction.

Paradoxically, discussion of renal hypertension requires mention of its negation, renoprival hypertension. This term applies to the hypertension consequent on total or nearly total deprivation of renal tissue, best demonstrated in animals maintained alive by vividialysis. The pressure levels reached are not very high, and the process is associated with disproportionately severe acute arterial necroses. The condition is attributed to deprivation of a renal antipressor function[78] which may be mediated through the adrenal,[79] is partially sodium-dependent, and is quite distinct from the renin mechanism.[80] It is one of the facts that support Braun-Menéndez's inclusive hypothesis[81] of a renotrophic origin of both renal and renoprival hypertension. Clinically, the renoprival mechanism — whatever it may be — probably contributes to hypertension and vascular lesions in terminal renal disease and in the acute tubular necroses.

## RECAPITULATION

Before starting on a discussion of essential hypertension — that bourn from which few travellers intelligibly return — it might be useful to sum up key points of what has been said. In brief, experimental hypertensions have been produced by means that involve at least four systems; these are neural, endocrine, vascular and renal; each experimental hypertension has a clinical equivalent. The primary mechanisms of each of these differ; secondarily, however, each seems to involve the other, so that, for example, hypertension which is initially renal becomes secondarily sustained by neural, endocrine and doubtless vascular components. These secondary mechanisms explain the tendency of some remediable hypertensions to persist after removal of their primary cause, causing them to become self-sustaining and self-aggravating. The clinical corollary is that cure of secondary hypertension depends very largely on prompt recognition of its nature and relief of its cause. Henry Mencken, inspired by "Popsy" Welch, felt that pathology would be a lovely science even if it had no therapeutic implications; correspondingly, the experimental pathology of the hypertensions is the more fascinating because it can be applied at the bedside as well as in the laboratory.

## ESSENTIAL HYPERTENSION

By definition, primary essential hypertension has no cause and no laboratory equivalent except as chance or selective breeding results in a spontaneous hypertension which, in dogs, is often renal.[82] Pickering's[2] concept is that "what is currently designated essential hypertension represents that section of the population having arterial pressures above an arbitrarily defined value. . . . If secondary hypertension is excluded, there is no evidence that high pressure is qualitatively different from normal arterial pressure, the difference is not of kind, but of degree." This statement in no way alters existing problems of etiology, diagnosis or treatment, since "expectation of life diminishes with the rise of arterial pressure"; explicit exclusion of secondary mechanisms is only metaphysically feasible, although the concept almost implies that imperceptibly these may arise at any time. Others[15] do not admit the assumption that numerical continuity necessarily or exclusively implies identity or eurhythmy of mechanisms, even when, as in essential hypertension, these are genetically conditioned. Thus, foot size, breast size, body height, tonsorial endowment, amorous susceptibility, blood sugar and lipid vary in continuous progressions but everyone recognizes that the variations include pathological degrees of each. Hence, this concept is more a description than

an explanation. Its advantage lies primarily in its contradiction of the futile, monistic approaches of the past; these have overemphasized the operation of abnormal, unusual or fanciful mechanisms and have neglected those that normally regulate arterial pressure: hence, Dr. Page's formulation of the "mosaic theory" of essential hypertension as a working hypothesis. This includes a kaleidoscopic pattern of displaced equilibria among the mechanisms that maintain normal and those that may abnormally increase arterial pressure.

In principle, this concept aims at serial, quantitative determinations of the various vectors that contribute to a persistent increase in arterial pressure. Unfortunately, these do not admit such tests at present. For example, pressor hyperresponsiveness is a common, but not invariable, characteristic of essential hypertension, but its components extend from the heart to the capillaries and throughout the nervous system and the body fluids and cannot be separately characterized. Nevertheless, a concept based on the hyperresponsiveness of the digital circulation to norepinephrine has been recently stated.[83] In some situations, trial of a specific therapeutic agent, such as an antiserum, has served as a diagnostic test. We have confidently hoped that this might be the case in essential hypertension. While the last decade has witnessed the introduction of a variety of useful drugs, each acting primarily on certain systems, none is sufficiently specific to serve as an etiological tool. Low-sodium dietotherapy is a possible exception. Some believe that it may act specifically on abnormalities in tissue electrolytes; unfortunately, easily measurable decreases in plasma volume may simply and adequately, if not exclusively, explain responses to such diets or to natriuretic drugs such as chlorothiazide. Still, the fact that favourable response to these regimens occurs only in a minority of patients[84, 85] does imply some etiological separation of these from other patients with essential hypertension who do not respond to similar measures.

Essential hypertension continues to defy the experimentalist. On the other hand, its disabling, fatal concomitant — hypertensive vascular disease — is accessible. In Bright's wake, opposing concepts of the nature of this association were formulated at Guy's by Gull and Sutton[86] and by Mahomed.[87] The debate has continued for 80 years and has not been fully resolved by 25 years' study of experimental hypertension. However, observations in rats[41, 88, 89] establish that maintenance of a pressure lower than systemic arterial pressure protects the renal arterioles from nephrosclerotic and necrotizing lesions. In acute experiments, brief bursts of increased arterial pressure and volume provoke acute renal arteriolar lesions.[90, 91] A more conclusive, quantitative study of the association has recently shown a close dependence of experimental hypertensive vascular disease on increased arterial pressure,[92, 93] so that it now seems definitely established that hypertension as such is a primary cause of hypertensive arteriolar disease.

Clinical studies are necessarily retrospective. However, these accord with the experimental findings in that they abundantly demonstrate that effective treatment of severe hypertensive states with antipressor agents — regardless of their nature — remits the signs of hypertensive vascular disease and, in some patients, results in striking recovery of renal and other functions.[94] One disparity between observations in patients and those in rats is that a considerable proportion of patients who have undergone remissions of severe hypertension succumb to complications of large-vessel arteriosclerosis — cerebral, cardiac, aortic and renal. This seems to be in part a species difference; however, as concerns the renal vascular bed, a correspondence can be established between the productive intimal changes that led to renal failure in some treated hypertensive patients and the lesions found in rats subjected to renal infarction and treated with antipressor drugs.[95]

Nearly 50 years ago Sir William Osler spoke of the "associations, advantages and disadvantages" of high blood pressure.[96] Many good observers[97, 98] have since drawn attention to the relatively benign course of most patients with mild or moderate hypertension, noting how some old ladies thrive on it. However, the advantages or uneventful character[98] of untreated "hyperpiesis" or "hypertonia" are not very real. The mortality tables speak for themselves, while the advantages of antihypertensive treatment can be demonstrated both in animals and in man. Particularly convincing of the value of such treatment is the experience[99] of a six-year survival of nearly a third of patients presenting the syndrome of malignant hypertension. Further, we are convinced that, with improved techniques, this score can be considerably bettered. It will require prolonged study of many patients with less severe hypertension to demonstrate a comparable, if less dramatic, beneficial effect. Pending such a demonstration, the desirability of antihypertensive measures in symptomless patients is still debated; a case can be made against "the manometric Procrustes" who disregards the cost and the unpleasant and hazardous effects of these drugs — and, with stereotyped mediocrity, treats the manometer.

## HOMŒOSTASIS OF HYPERTENSION

The therapist's point of view can be defended.[100] We have seen that experimentally a number of mechanisms can perpetuate hypertension after removal of its cause. Clinical experience in renal hypertension and in phæochromocytoma bears this out. Another instance is the recovery of arterial pressure to hypertensive levels in patients treated with an antiadrenergic agent; the adrenergic vasomotor component of the hypertension was suppressed, but some other pressor mechanism took

its place.[101] A recent, more dramatic example is the case of chlorothiazide potentiation of drugs that diminish vasomotor tone.[85] The sequence here is that natriuresis and diuresis decrease plasma volume; the homœostasis of arterial pressure – normotensive or hypertensive – reacts by increased vasomotor tone. If the ability to increase vasomotor tone has been impaired by concurrent administration of reserpine or a ganglion-blocker, the effectiveness of this agent is greater than it had been when plasma volume and vasomotor tone were within their former limits. The primacy of hypovolæmia in the sequence is suggested by changes in renal[102] and other hæmodynamic functions[85, 103] and particularly by restoration of control hæmodynamic status and reversal of chlorothiazide-sensitization following infusions of sodium-free dextran. Primacy, however, does not exclude the possibility that this and like regimens may act in part by modifying tissue sodium content and transport systems.

Chlorothiazide, then, provides another excellent but therapeutically advantageous example of the homœostasis of hypertension. This concept and its corollaries run in this way. Persistent arterial hypertension tends to be self-sustaining or homœostatic. Secondary mechanisms, notably renal, contribute to this, activated by hypertensive vascular disease and, sometimes, atherosclerosis. However, since blood pressure tends to persist at whatever level it is stabilized at for long periods, early treatment that maintains normal pressure levels for long periods should suppress and even cure mild just as it palliates severe hypertension. The validation of this concept and its corollary requires attention, care, cost, possibly better and more specific agents than are now available and certainly more evidence than can be adduced. However, as Stewart[104] has pointed out, "for the first time since Stephen Hales so alarmed his horse, there is appearing real hope of lasting benefit for many thousands of men and women whose lives have hitherto been under constant threat of death or damage". This, even though we do not yet have full insight into ultimate causes or specific treatment, is a cheerful prospect indeed. What I have tried to show is that the knowledge and ability we now possess owe much to and expect more from the continued study of the experimental hypertensions to which Dr. Braun-Menéndez made such notable contributions.

## REFERENCES


1. MASTER, A. M., GARFIELD, C. L. AND WALTERS, A. M.: Normal Blood Pressure and Hypertension, Lea & Febiger, Philadelphia, 1952.
2. PICKERING, G. W.: High Blood Pressure, Grune & Stratton, New York, 1955.
3. ROBINSON, S. C. AND BRUCER, M.: *Arch. Int. Med.*, **64**: 409, 1939.
4. Conference on Longitudinal Cardiovascular Studies, Brookline, Massachusetts, June 1957.
5. PAGE, I. H. AND CORCORAN, A. C.: Arterial Hypertension, 2nd ed., Year Book Publishers, Inc., Chicago, 1949.
6. CORCORAN, A. C., DUSTAN, H. P. AND PAGE, I. H.: *Ann. Int. Med.*, **43**: 1161, 1955.
7. KOCH, E. AND MIES, H.: *Krankheitsforschung*, **7**: 241, 1929.
8. LENNARD, H. L. AND GLOCK, C. Y.: *J. Chron. Dis.*, **5**: 186, 1957.
9. SCHNECKLOTH, R. E., STUART, K. AND CORCORAN, A. C.: Manuscript in preparation.
10. HARRIS, R. E. *et al.*: *Circulation*, **7**: 874, 1953.
11. WOLF, S. G. *et al.*: Life Stress and Hypertension, Williams and Wilkins Co., Baltimore, 1955.
12. ROTHLIN, E., CERLETTI, A. AND EMMENEGGER, H.: *Acta med. scandinav.*, (Supp. 312) **154**: 27, 1956.
13. SIMONSON, E. AND BROZEK, J.: *Ann. Int. Med.*, **50**: 129, 1959.
14. PAGE, I. H., MCCUBBIN, J. W. AND CORCORAN, A. C.: *Perspectives Biol. Med.*, **1**: 307, 1958.
15. CORCORAN, A. C. *et al.*: *Am. J. Med.*, **17**: 383, 1954.
16. BRODIE, B. B.: Hypertension, Am. Heart Assoc., New York, 1959.
17. EVELYN, K. A., ALEXANDER, F. AND COOPER, S. R.: *J. A. M. A.*, **140**: 592, 1949.
18. SMIRK, F. H.: High Arterial Pressure, Charles C Thomas, Springfield, Ill., 1957.
19. MCCUBBIN, J. W.: *Circulation*, **17**: 791, 1958.
20. SELYE, H.: *J. Clin. Endocrinol.*, **6**: 117, 1946.
21. MASSON, G. M. C. *et al.*: *A.M.A. Arch. Path.*, **49**: 641, 1950.
22. SELYE, H.: The Physiology and Pathology of Exposure to Stress: A Treatise Based on the Concepts of the General-Adaptation Syndrome and the Diseases of Adaptation. Acta, Inc., Montreal, 1950.
23. KUMAR, D. *et al.*: *Canad. J. Biochem. Physiol.*, **35**: 113, 1957.
24. CONN, J. W.: *J. Lab. & Clin. Med.*, **45**: 3, 1955.
25. DUSTAN, H. P., CORCORAN, A. C. AND PAGE, I. H.: *J. Clin. Invest.*, **35**: 1357, 1956.
26. SKELTON, F. R.: *Physiol. Rev.*, **39**: 162, 1959.
27. MASSON, G. M., KORITZ, S. B. AND PERON, F. G.: *Endocrinology*, **62**: 229, 1958.
28. GENEST, J. *et al.*: *Proc. Soc. Exper. Biol. & Med.*, **97**: 676, 1958.
29. DUSTAN, H. P., MASON, H. L. AND CORCORAN, A. C.: *J. Clin. Invest.*, **32**: 60, 1953.
30. COOPER, D. Y. *et al.*: *Ibid.*, **37**: 1524, 1958.
31. JEFFERS, W. A. *et al.*: *J. A. M. A.*, **153**: 1502, 1953.
32. FRIEDMAN, S. M. AND FRIEDMAN, C. L.: *Canad. M. A. J.*, **61**: 596, 1949.
33. PRADO, J. L.: Estudos sobre hipertensa experimental. Thesis, Escola Paulista de Medicina, Sao Paulo, Impressora Ipsis, 1959.
34. STURTEVANT, F. M.: *Ann. Int. Med.*, **49**: 1281, 1958.
35. FARRELL, G., KOLETSKY, S. AND LAPHAM, L. W.: *Fed. Proc.*, Part I, **18**: 44, 1959.
36. BALZER, R. AND MCCULLAGH, E. P.: *Am. J. M. Sc.*, **237**: 449, 1959.
37. MASSON, G. M., CORCORAN, A. C. AND PAGE, I. H.: *Endocrinology*, **61**: 409, 1957.
38. FRIEDMAN, S. M., JAMIESON, J. D. AND FRIEDMAN, C. L.: *Circulation Res.*, **7**: 44, 1959.
39. MASSON, G. M., CORCORAN, A. C. AND HUMPHREY, D. C.: *J. A. M. A.*, **165**: 1555, 1957.
40. DUSTAN, H. P. AND MASSON, G. M.: *Circulation*, **17**: 765, 1958.
41. LEDINGHAM, J. M. AND FLOYER, M. A., cited by WILSON, C.: *Lancet*, **2**: 579, 632, 1953.
42. GROSS, F.: *Klin. Wchnschr.*, **36**: 693, 1958.
43. MENEELY, G. R., BALL, C. O. AND YOUMANS, J. B.: *Ann. Int. Med.*, **47**: 263, 1957.
44. DAHL, L. K.: *Am. J. Clin. Nutrition*, **6**: 1, 1958.
45. FRIEDMAN, S. M., BUTT, R. M. AND FRIEDMAN, C. L.: *Am. J. Physiol.*, **190**: 507, 1957.
46. MCCUBBIN, J. W. AND PAGE, I. H.: *Circulation Res.*, **2**: 35, 1954.
47. TOBIAN, L.: *Ibid.*, **4**: 671, 1956.
48. BRIGHT, R.: *Guy's Hosp. Rep.*, **1**: 380, 1836.
49. BROCK, SIR RUSSELL, ed.: *Ibid.*, **107**: 263, 1958.
50. GOLDBLATT, H. *et al.*: *J. Exper. Med.*, **59**: 347, 1934.
51. SKEGGS, L. T., JR. *et al.*: *Ibid.*, **106**: 439, 1957.
52. SKEGGS, L. T., JR., KAHN, J. R. AND SHUMWAY, N. P.: *Ibid.*, **103**: 295, 1956.
53. BRAUN-MENÉNDEZ, E. AND PAGE, I. H.: *Science*, **127**: 242, 1958.
54. PAGE, I. H. AND HELMER, O. M.: *J. Exper. Med.*, **7**: 29, 1940.
55. BRAUN-MENÉNDEZ, E. *et al.*: *J. Physiol.*, **98**: 283, 1940.
56. BRAUN-MENÉNDEZ, E. *et al.*: Renal Hypertension, Charles C Thomas, Springfield, Ill., 1946.
57. SKEGGS, L. T., JR. *et al.*: *J. Exper. Med.*, **104**: 193, 1956.
58. SCHWARZ, H., BUMPUS, F. M. AND PAGE, I. H.: *J. Am. Chem. Soc.*, **79**: 5697, 1957.
59. ELLIOTT, D. F. AND PEART, W. S.: *Biochem. J.*, **65**: 246, 1957.
60. WAKERLIN, G. E.: *Physiol. Rev.*, **35**: 555, 1955.
61. ASK-UPMARK, E.: *Acta path. et microbiol. scandinav.*, **6**: 383, 1929.
62. WEISS, S., PARKER, F., JR. AND ROBB, G. P.: *Ann. Int. Med.*, **6**: 1599, 1933.
63. KIMMELSTIEL, P. AND WILSON, C.: *Am. J. Path.*, **12**: 99, 1936.
64. RAASCHOU, F.: Chronic pyelonephritis, E. Munksgaard, Copenhagen, 1948.
65. BROD, J.: Chronic pyelonefritis, Thomayerova Sbirka, Prague, 1956.
66. SOUTHWOOD, A. R.: *Lancet*, **1**: 377, 1959.
67. KINCAID-SMITH, P.: *Ibid.*, **2**: 1263, 1955.
68. FISHER, E. R. AND CORCORAN, A. C.: *A.M.A. Arch. Int. Med.*, **89**: 843, 1952.
69. POUTASSE, E. F. *et al.*: *J. A. M. A.*, **161**: 419, 1956.
70. BRUST, A. A. *et al.*: *J. Clin. Invest.*, **37**: 882, 1958.
71. POUTASSE, E. F. AND DUSTAN, H. P.: *J. A. M. A.*, **165**: 1521, 1957.
72. DUSTAN, H. P. AND POUTASSE, E. F.: *Heart Bull.*, **7**: 117, 1958.
73. WINTER, C. C. AND TAPLIN, G. V.: *J. Urol.*, **79**: 573, 1958.
74. CONNOR, T. B. *et al.*: *Bull. Johns Hopkins Hosp.*, **100**: 241, 1957.
75. KLAPPROTH, H., TAKAGI, H. AND CORCORAN, A. C.: Manuscript submitted for publication.

76. DUSTAN, H. P. *et al.*: Manuscript submitted for publication.
77. POUTASSE, E. F.: Manuscript submitted for publication.
78. GROLLMAN, A., MUIRHEAD, E. E. AND VANATTA, J.: *Am. J. Physiol.*, 157: 21, 1949.
79. LEDINGHAM, J. M.: *Clin. Sc.*, 10: 423, 1951.
80. KOLFF, W. J.: *Cleveland Clin. Quart.*, 24: 141, 1957.
81. BRAUN-MENÉNDEZ, E.: *Ann. Int. Med.*, 49: 717, 1958.
82. MCCUBBIN, J. W. AND CORCORAN, A. C.: *Proc. Soc. Exper. Biol. & Med.*, 84: 130, 1953.
83. MENDLOWITZ, M., GITLOW, S. AND NAFTCHI, N.: Cause of primary hypertension, paper presented at Scientific Sessions, American Heart Association, San Francisco, Oct. 24, 1958.
84. CORCORAN, A. C., TAYLOR, R. D. AND PAGE, I. H.: *Circulation*, 3: 1, 1951.
85. DUSTAN, H. P. *et al.*: *Ibid.*, 19: 360, 1959.
86. GULL, W. W. AND SUTTON, H. G.: *Med.-chir. Trans.*, 55: 273, 1872.
87. MAHOMED, F. A.: *Ibid.*, 57: 197, 1874.
88. WILSON, C. AND BYROM, F. B.: *Quart. J. Med.*, 10: 65, 1941.
89. SELYE, H. AND STONE, H.: *J. Urol.*, 56: 399, 1946.
90. BYROM, F. B. AND DODSON, L. F.: *J. Path. & Bact.*, 60: 357, 1948.
91. MASSON, G. M., CORCORAN, A. C. AND PAGE, I. H.: *Rev. canad. biol.*, 10: 309, 1951.
92. MASSON, G. M., CORCORAN, A. C. AND PAGE, I. H.: *Cleveland Clin. Quart.*, 26: 24, 1959.
93. MASSON, G. M. *et al.*: *Am. J. Path.*, 34: 817, 1958.
94. CORCORAN, A. C. AND PAGE, I. H.: *M. Clin. North America*, 39: 1027, 1955.
95. MCCORMACK, L. J. *et al.*: *Am. J. Path.*, 34: 1011, 1958.
96. OSLER, W.: *Brit. M. J.*, 2: 1173, 1912.
97. PERERA, G. A.: *J. Chron. Dis.*, 1: 33, 1955.
98. EVANS, W.: *Lancet*, 2: 53, 1957.
99. DUSTAN, H. P. *et al.*: *Circulation*, 18: 644, 1958.
100. DUSTAN, H. P. AND CORCORAN, A. C.: *Lancet*, 2: 601, 1957.
101. CORCORAN, A. C., TAYLOR, R. D. AND HARRISON, M.: *Proc. Soc. Exper. Biol. & Med.*, 80: 265, 1952.
102. CORCORAN, A. C. *et al.*: *Circulation*, 19: 355, 1959.
103. FREIS, E. F.: Actions of chlorothiazide in hypertensive patients. Proc. Council High Blood Pressure Res. (Cleveland, Ohio, Nov. 1958). In: *Hypertension*, Am. Heart Assoc., New York, 1959.
104. STEWART, I. M.: *Lancet*, 2: 753, 1957.

This bibliography would be incomplete without a reference to the inclusive *Hypertension: The First Hahnemann Symposium on Hypertensive Disease*, J. H. Moyer, ed., W. B. Saunders Company, Philadelphia, 1959.

## RÉSUMÉ

Dans cette conférence prononcée en hommage posthume au docteur Eduardo Braun-Menéndez, l'auteur fait remarquer que l'hypertension et l'artériosclérose sont responsables de 90% de la mortalité relevant du système cardio-vasculaire. Les victimes qui en sont atteintes et qui survivent n'en portent pas moins un lourd fardeau. Aucune des définitions actuelles de l'hypertension ne donne une véritable représentation de l'état de choses réel, elles se limitent à quelques chiffres sans application universelle à cause des différences raciales. On est d'accord cependant qu'il existe un point où en dépit des variations, la tension artérielle se maintient à un niveau anormalement élevé. Chez un petit nombre de malades l'hypertension peut être décrite d'une manière étiologique aussi bien que clinique. Ces formes dites secondaires comprennent les hypertensions d'origine neurogène, endocrine, vasculaire et rénale; un examen critique montre cependant qu'elles ne sont pas aussi individualisées qu'on serait porté à le croire de prime abord.

L'expérience classique en hypertension neurogène date de 1929 avec la résection des nerfs sino-aortiques qui déclenche une forte augmentation du tonus vaso-moteur. Cette réaction semble correspondre à une libération constante de norépinéphrine. Cushing a montré qu'une augmentation soudaine de la tension intracranienne provoque une hypertension plus ou moins prolongée. L'intuition profane relie souvent la tension artérielle aux états de tension psychologique. Les résultats des recherches dans ce sens n'ont réussi à prouver qu'une tension psychique peut mettre en évidence certaines tendances latentes à l'hypertension. Certains voient dans l'action de la réserpine une preuve du rôle que joue la tension psychologique dans l'étiologie de l'hypertension. Cependant les preuves s'accumulent à l'effet que les doses employées dans le traitement de l'hypertension pourraient avoir un effet sympatholytique et vasodilatateur qui suffirait amplement à expliquer son efficacité dans ces circonstances. On a invoqué certains troubles de fonction des récepteurs de pression dans l'étiologie de l'hypertension. Il semblerait possible en effet que pour une cause encore inconnue ce mécanisme soit ajusté à un niveau de tension plus élevé que la normale. Cependant il semble que ce système aurait plutôt tendance à maintenir élevée une tension qu'auraient déjà augmentée certains agents rénaux et endocriniens.

Au point de vue biologique, les hormones seraient les ancêtres des mécanismes de réaction nerveuse au milieu ambiant. Il n'est donc pas étonnant qu'il existe un certain degré de chevauchement entre ces deux systèmes, que l'on retrouve entre autre dans l'hypertension. Les travaux classiques de Selye présentant l'hypertension comme une maladie de l'adaptation ne sont pas acceptés de tous parce que le problème dépasse à la fois l'explication et les faits observés. Cependant ces travaux sont à l'origine de la différence établie depuis entre l'hypertension causée par les gluco- et les minéralo-corticoïdes et celle causée par l'aldostérone. L'hypertension qui suit l'hypofonction corticale des surrénales n'a jusqu'à présent reçu aucune explication. On a aussi décrit une forme d'hypertension qui suit l'administration de désoxycorticostérone; l'intérêt de cette manifestation réside en sa tendance à se perpétuer après la suppression de sa cause. Les facteurs qui relèvent de la pituitaire, des surrénales et de la thyroïde semblent d'ordre secondaire et ne se rangent pas parmi les causes primaires de l'hypertension chez l'humain. La liste des facteurs endocriniens comme cause d'hypertension ne serait complète sans la mention des tumeurs phéochromocytomes qui sans être fréquentes ne sont tout de même pas rares. L'effet natriurétique de la rénine produit une hypertrophie de la *zona glomerulosa* des surrénales. L'hypertension endocrinienne chez le rat dépend intimement de l'ingestion de sel; son équivalent peut se retrouver chez l'homme puisqu'au niveau tissulaire les ions de sodium peuvent servir comme agent de certaines amines hypertensives, de l'angiotensine, de la pitressine et de certains stéroïdes.

Parmi les facteurs vasculaires d'hypertension la correction de la coarctation de l'aorte a rendu le diagnostic de cette anomalie encore plus important. L'hypertension qui résulte de la perte d'élasticité des gros vaisseaux causée par l'artériosclérose est une forme connue et bénigne que le médecin doit savoir reconnaître afin d'éviter de créer de l'angoisse chez ses malades âgés.

L'importance du rein dans l'étiologie de l'hypertension fut reconnue il y a cent ans par Richard Bright, mais ce n'est qu'en 1933 que ces observations prirent l'ampleur qu'on leur connaît maintenant ávec le travail de Goldblatt. La participation rénale débute avec la libération dans le plasma d'un enzyme catheptique, la rénine provenant de l'appareil juxtaglomérulaire, dès que la circulation rénale est diminuée. Dans le flux plasmatique, la rénine agit sur un groupe particulier de globuline alpha-2 spécifique que l'on désigne comme substrat de la rénine ou encore angiotensinogène ou hypertensinogène pour en isoler un polypeptide formé de dix acides aminés et inerte au point de vue vasculaire, l'angiotensine I. Un autre enzyme plasmatique spécifique dit "convertisseur" retranche deux acides aminés de l'angiotensine I et donne l'angiotensine II, un polypeptide formé de huit acides aminés, possédant une action vasculaire puissante et jadis connu sous le nom d'angiotonine ou hypertensine. Des enzymes protéolytiques en provenance de plusieurs tissus, dont le rein, fractionnent l'angiotensine II en résidu inactif, et ces enzymes sans être spécifiques ni semblables peuvent être groupées pour fins pratiques sous le signe de cette caractéristique comme *angiotensinase*.

L'auteur relate dans ses grandes lignes les principales étapes qui ont marqué au cours d'un demi-siècle la découverte de ce système. Parmi les hypertensions d'origine rénale celles dues à la pyélo-néphrite se prêtent bien à un diagnostic précoce et à un traitement prophylactique adéquat. L'application clinique de la découverte de Goldblatt a dû attendre la mise au point d'une technique pratique d'angiographie rénale. Alors qu'on en avait décrit aucun cas jusqu'en 1950 à la clinque de Cleveland, 48 cas furent traités en 1957 et en 1958. Les signes qui laissent soupçonner la présence d'une lésion artérielle sont l'inégalité dans le volume des deux reins et dans leurs fonctions excrétoires, telles qu'observées à l'urographie ou au moyen de rénogrammes par radio-isotopes, particulièrement en l'absence d'antécédents familiaux; une hypertension d'origine récente et de progression rapide surtout chez un malade de moins de 35 ans ou de plus de 60 et l'association d'hypertension avec douleur dans le flanc. Des considérations sont ensuite données sur l'interprétation des différentes épreuves employées dans le dépistage de ces lésions. La découverte de ces lésions a permis un traitement chirurgical de l'hypertension chez un nombre de malades grandissant chaque année. Ces interventions comprennent la résection et l'anastomose, l'endartérectomie ou la greffe dans les lésions

de l'artère rénale, la néphrectomie segmentaire ou partielle lorsqu'une branche seulement de cette artère est atteinte et lorsque les mesures conservatrices ne s'appliquent plus, la néphrectomie unilatérale. Des lésions simulant une réaction de Shwartzman accélérée ont été créées chez les rats traités aux stéroïdes ou à l'hormone de croissance, ou soumis à l'énucléation des surrénales, à qui on donna ensuite de la rénine. Ces lésions rappellent celles de la toxémie de la grossesse ou de la lupo-viscérite. L'hypertension rénoprive d'envergure plus modeste se voit chez les animaux maintenus en vie par la vividialyse. On l'attribue à la privation du facteur rénal antihypertensif qui peut se manifester par l'entremise des surrénales, dépendant en partie du sodium et sans relation avec le mécanisme de la rénine.

Par définition l'hypertension essentielle n'a pas de causes ni d'équivalent expérimental sauf lorsque la chance ou le croisement dirigé produit une hypertension spontanée qui chez le chien est souvent d'origine rénale.

Selon la théorie de la "mosaïque" du Dr. Page, l'hypertension artérielle représenterait une série d'équilibres déplacée, rétablis à d'autres niveaux, parmi les mécanismes qui conservent la tension normale et ceux qui peuvent l'augmenter à un niveau anormal. Les facteurs en jeu se prêtent mal à la mensuration. L'étiologie de l'hypertension essentielle n'est pas nécessairement unique puisque la seule mesure qui montre quelque spécificité, la diète désodée, agit chez certains malades et non chez d'autres. Il semble bien établi que l'hypertension est la cause primordiale de la maladie artériolaire hypertensive. Toute mesure qui tend à abaisser la tension retarde de développement des lésions et améliore la fonction rénale. L'efficacité de ce traitement se lit dans la survie de six ans de près d'un tiers des malades atteints d'hypertension maligne et soumis à ces mesures. On discute encore de l'opportunité d'administrer ces médicaments aux hypertendus asymptomatiques; l'auteur désavoue les Procustes du manomètre. Cependant comme la tension artérielle tend à se stabiliser à quelque niveau que ce soit où elle a été maintenue pendant assez longtemps, souhaitons que les chercheurs explorent cette avenue de la thérapeutique pour nous en rapporter de nouvelles données et de nouveaux médicaments.

---

## THE FINE STRUCTURE OF PLASMA CELLS IN RELATION TO THEIR FUNCTION*

HENRY Z. MOVAT, M.D., Ph.D.,† and DOUGLAS R. WILSON,‡ *Toronto*

THE FINDINGS to be reported deal with the fine structure of plasma cells which develop in rabbits after immunization. Development of plasma cells in the spleen was induced by the injection of foreign protein. Animals were killed when plasma cell proliferation was at its height.[14]

### MATERIALS AND METHODS

Three albino rabbits, weighing 2.5 kg. on the average were injected intravenously with 10 ml./kg. sterile horse serum on the first day of the experiment and again with the same amount of antigen one month later. Two animals were killed five days and one seven days after the last dose of antigen.

Three additional rabbits received weekly intraperitoneal injections of 2.0-5.0 ml. of dog kidney homogenate (approx. 20%) in normal saline for a period of two months. All were killed one week after the last injection. They were part of a group used for the production of nephrotoxic serum; the latter was used in another experiment.

Fragments of spleen were fixed in 10% buffered (pH 7) formalin and Zenker-formol for light microscopic studies and in Palade's buffered (pH 7.4) osmium tetroxide for electron microscopic studies. Tissue for the former was embedded in either paraffin or plastic (butyl and methyl methacrylate), cut at 0.5–4 micra, and stained with May Grünwald-Giemsa, azure eosin, or methyl green-pyronin. Selected sections were stained with periodic acid-Schiff (for reticular fibres) and counterstained with azure A or with periodic acid silver methanamine (for the demonstration of plasma cells in very thin sections). For electron microscopy the tissues were embedded in butyl and methyl methacrylate (8:1) and cut with a Porter Blum microtome. Sections were examined with a RCA-EMU-2 electron microscope.

### RESULTS

The spleen of the normal rabbit is composed of red and white pulp. The former has a framework of reticular fibres forming sinusoids which are lined by reticulo-endothelial or littoral cells. The reticular fibres between sinusoids form the pulp cords, which enclose reticular and other cells. The white pulp, which is composed of lymphocytes and reticular cells, forms sleeves around arteries. Larger aggregates of the white pulp form the follicles. The periphery of a lymph follicle is composed of medium-sized lymphocytes and the central part of small lymphocytes. A "germinal centre" made up of blast cells, mainly lymphoblasts, may be present in a follicle.

Plasma cells develop at the periphery of lymphoid tissue, i.e., at the border between white and red pulp. As they increase in number they become separated from the white pulp by proliferating lymphocytes. Thus, small groups of plasma cells are found in the red pulp, while larger accumulations are encountered in the peripheral parts of the white pulp (Figs. 1-3). With repeated small doses of antigen, plasma cells may develop in the centre of follicles as well.

At high power, plasma cells are quite characteristic. They have an eccentrically situated nucleus and abundant basophilic or pyroninophilic

---

*From the Department of Pathology, University of Toronto, the Banting Institute, Toronto, Ontario.
Supported by a grant from the National Research Council of Canada.
†Assistant Professor of Pathology, University of Toronto; Senior Research Fellow, Canadian Arthritis and Rheumatism Society.
‡Fourth-Year Medical Student, Lederle Undergraduate Research Fellow.

cytoplasm and many of them show a juxtanuclear halo, corresponding to the Golgi complex or apparatus. Immature forms, i.e., plasmablasts and proplasmacytes, have large vesicular nuclei and less cytoplasm in relation to the nucleus. Most cells are oval; others are irregular owing to compression resulting from crowding in groups. Thin sections, cut at 0.5 micron and impregnated with silver methanamine, show some detail in the cytoplasm (Fig. 4), in contrast to sections stained by the usual techniques where it appears homogeneous. However, the resolution of the light microscope does not permit a clear recognition of cytoplasmic details.

A low-power view of an electron micrograph (Fig. 5) shows at a first glance that the plasma cells are easy to recognize. To the right there is a sinusoid lined by littoral cells, some with and others without nuclei (in the latter the nuclei were not in the plane of section). Part of a red cell is present in the sinusoid and some are also seen between the cells of the red pulp. The granular material in the sinusoid is precipitated plasma protein. The cells at the top and one to the left of centre are macrophages. They all have pale nuclei and abundant cytoplasm. A Golgi apparatus and several mitochondria can be seen in the macrophage in the centre. Above this macrophage there are two lymphocytes with irregular nuclei and only a few mitochondria in their cytoplasm. About one-third of the lower part of the photograph is occupied by plasma cells. The cytoplasm of plasma cells is characteristic. It contains numerous so-called rough-surfaced vesicles or endoplasmic reticulum. In addition one can recognize round or oval mitochondria, and in one cell the Golgi apparatus is well demonstrated. The cells with larger and less dense nuclei are proplasmacytes. A cell in the centre seems to be undergoing amitotic division. Plasma cells with two nuclei are known to occur commonly.

Fig. 6 is a very high-power view which shows the detail of the cytoplasm in a mature plasma cell. The mitochondria with their cristæ are well recognized at this power. The rough-surfaced vesicles (endoplasmic reticulum) vary in size and shape, but most of them appear dilated. They are coated by ribonucleic acid granules, which are also found between the vesicles. The vesicles contain a moderately osmophilic substance marked "GG(?)", which likely represents gamma globulin.

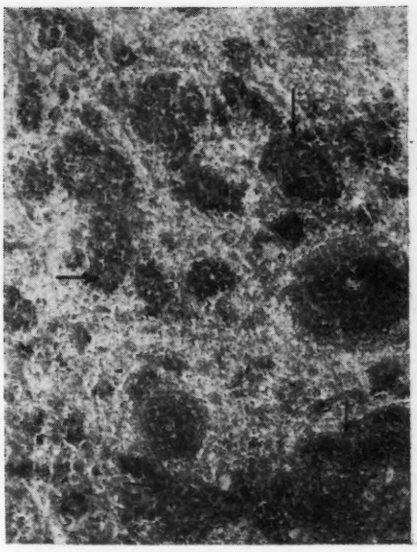


Fig. 1

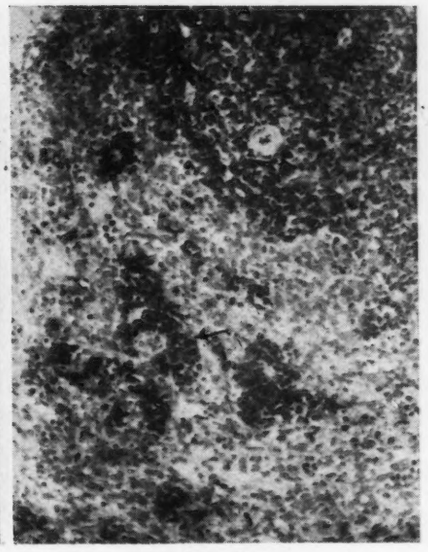


Fig. 2

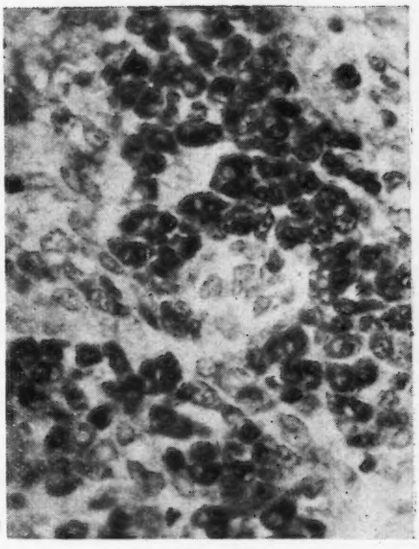


Fig. 3

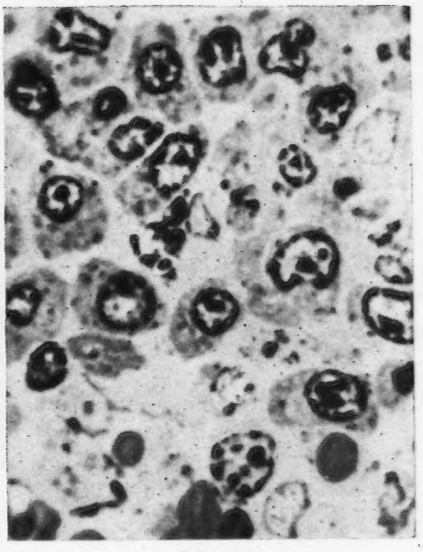


Fig. 4

**Fig. 1.**—Very low-power photomicrograph of spleen showing varying-sized groups of plasma cells, represented by the black areas (which were red in the slide). They are found mainly at the periphery of the white pulp (arrow). 5 $\mu$ section, methyl green-pyronin, × 53.

**Fig. 2.**—About one-quarter (upper right) of this low-power photomicrograph is composed of a lymph follicle; the remainder is red pulp. Plasma cells are seen in varying-sized groups in the red pulp and as an outer rim around the lymph follicle. 5 $\mu$ section, methyl green-pyronin, × 100.

**Fig. 3.**—Higher magnification of a group of plasma cells seen in Fig. 2 (arrow). × 450.

**Fig. 4.**—High-power photomicrograph of a group of plasma cells. Those with larger, less dense nuclei are proplasmacytes. The nuclei are characterized by peripheral distribution of the chromatin. Some detail is discernible in the cytoplasm. The round globules are mitochondria. ½ $\mu$ section, periodic acid-silver methanamine, × 1575.

## Discussion

Plasma cells are known to manufacture antibody.[2, 6, 8, 9, 11, 12, 21] Upon systemic injection of antigen they develop and proliferate mainly in the spleen and lymph nodes.[2, 8, 9, 11, 14] However, if large doses of antigen are injected, plasma cells develop throughout the connective tissue. In the latter situation it is mainly a perivascular prolifer-

Canad. M. A. J.
Aug. 1, 1959, vol. 81

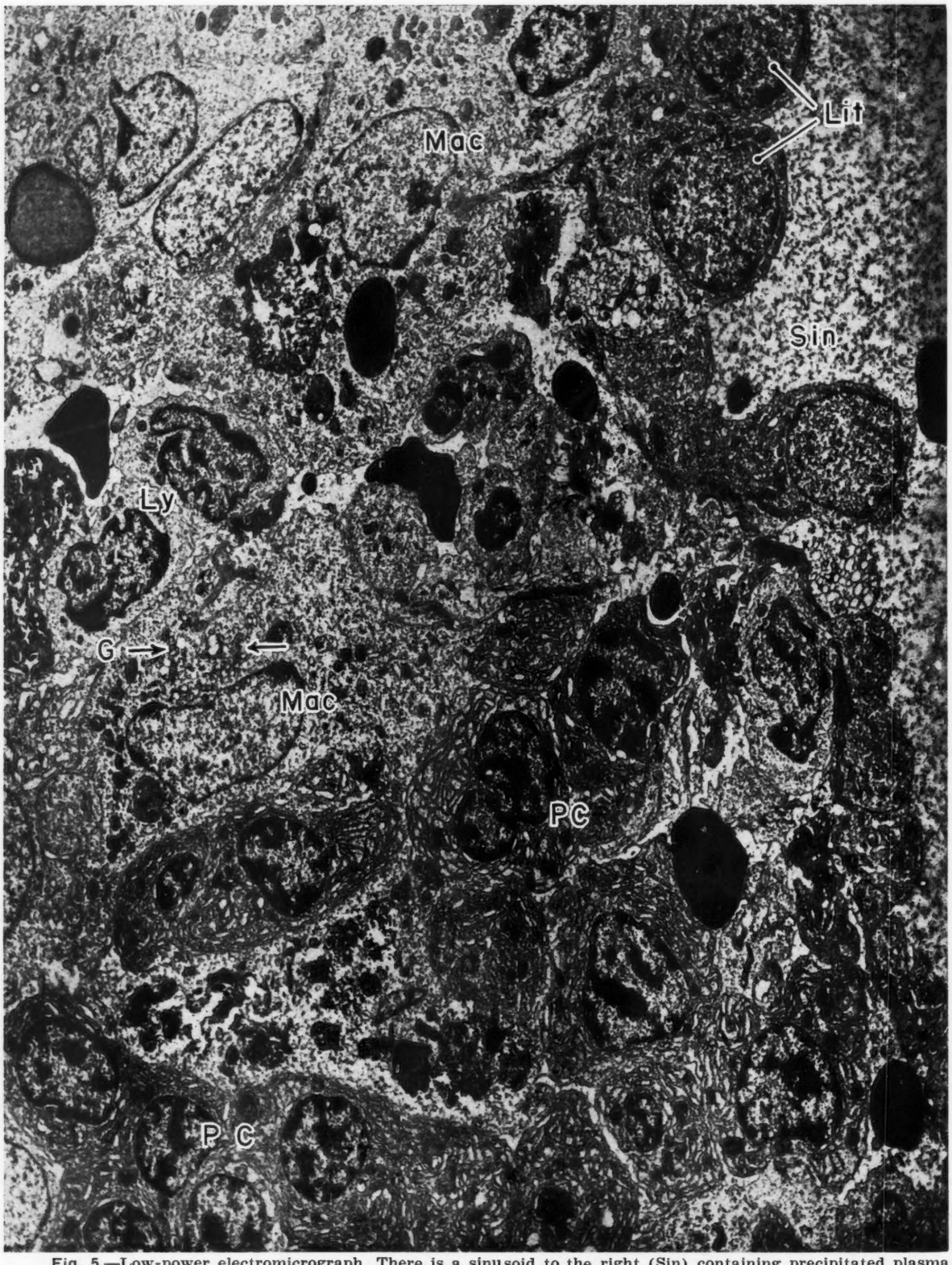



Fig. 5.—Low-power electromicrograph. There is a sinusoid to the right (Sin) containing precipitated plasma (granular material) and part of a red cell. The sinusoid is lined by littoral cells (Lit), some of which are vacuolated. Two macrophages are seen in the pulp cord (Mac). They contain numerous mitochondria (round bodies). The one located left of centre has a prominent Golgi apparatus (G) above the nucleus. It also contains phagocytized material (round globule below nucleus). Above the macrophage there are two lymphocytes (Ly). Plasma cells (P.C.) occupy the lower half of the photograph. They are characterized by dense nuclei and abundant endoplasmic reticulum (rough-surfaced vesicles) in their cytoplasm. The Golgi apparatus is seen in the plasma cell below the macrophage. Mitochondria are present in plasma cells in moderate numbers (compare with Figs. 4 and 6). The cell in the centre seems to be undergoing amitotic division. The round, oval and irregular homogeneous dark grey to black bodies in the pulp cord are red cells. Some appear smaller because they have been cut tangentially. × 5000.

ation.[12, 14] Local injection of antigen is followed by proliferation of plasma cells in regional lymph nodes[6, 22] while local (skin, joint, pleura) injection in a previously immunized animal also causes an intense proliferation of these cells *in situ* (the Arthus phenomenon).[12, 15]

Most textbooks of histology, pathology and hæmatology still describe the lymphocyte as the

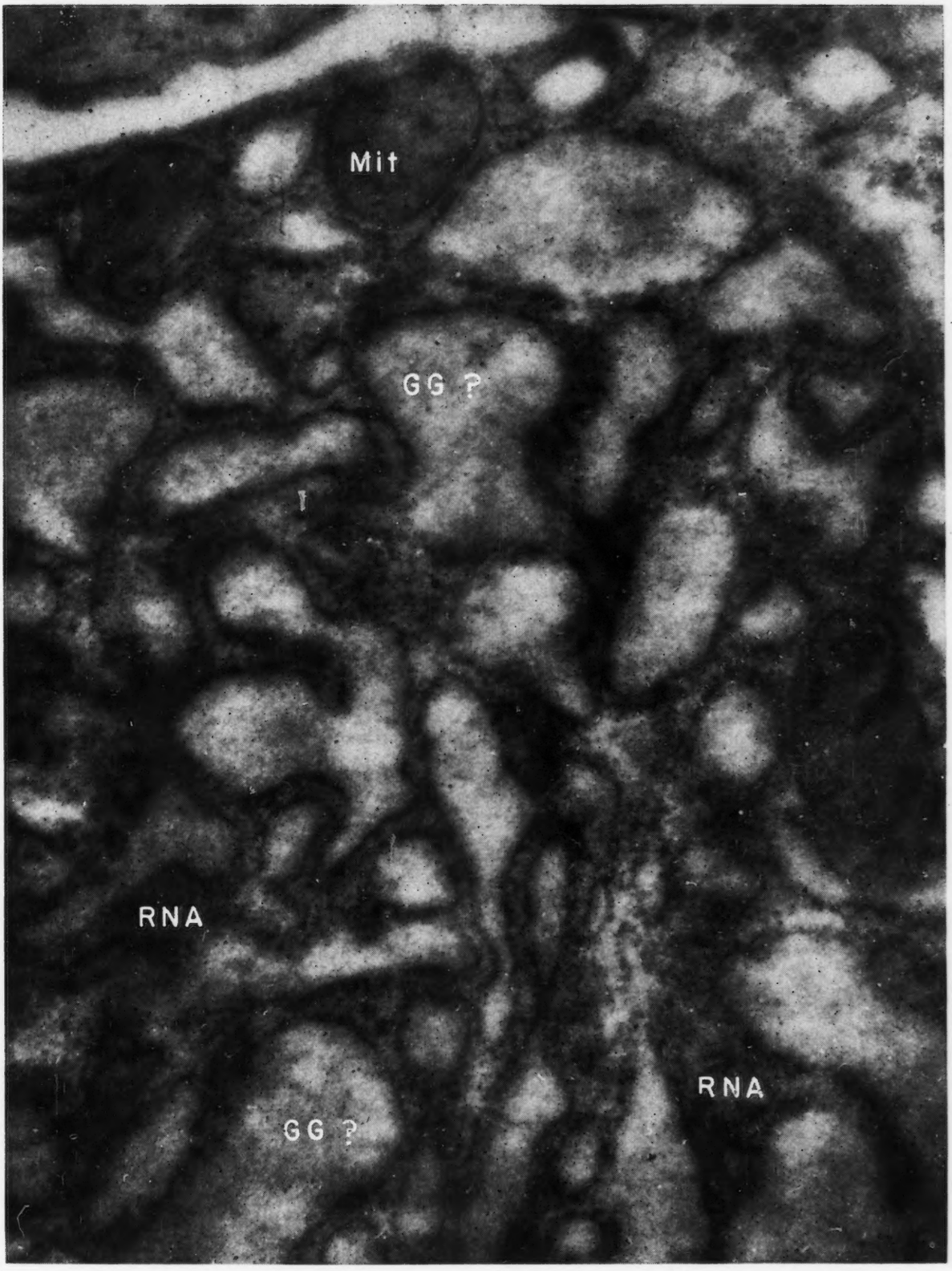



Fig. 6.—High-power electron micrograph showing a portion of the cytoplasm of a plasma cell. There are numerous irregular rough-surfaced vesicles, coated by RNA granules, and there are also RNA granules between the vesicles. The vesicles contain a moderately osmophilic material (G.G.?), representing probably gamma globulin. Three mitochondria (Mit) are seen. The one in the right upper corner has distinct cristæ mitochondriales. × 61,500.

precursor cell of the plasma cell, first suggested by Marschalko. There is now some evidence that they develop from primitive reticulum cells in the hæmopoietic tissues[8] and from primitive (predominantly perivascular) mesenchymal cells in connective tissue.[15] The latter has also been suggested by Ehrich[7] in his "Genetic theory of antibody production".

The significance of plasma cells in human pathology lies in the fact that plasma cells which

occur abundantly in lesions of experimental serum sickness are also encountered in lesions of the rheumatic or so-called collagen diseases. The former is known to develop on the basis of hypersensitivity. The latter is also believed to develop in a similar way. The finding of plasma cells was interpreted as representing indirect morphological evidence of an immune mechanism operating in both conditions.[12-14]

Although the various cells occurring in hæmopoietic tissues are one of the most thoroughly studied fields in electron microscopy, only a very few papers deal with the plasma cell. This is explained perhaps by the fact that hæmopoietic cells were studied mainly in human bone marrow, where there are relatively few plasma cells.

Braunsteiner *et al.*[3, 4] described plasma cells in the bone marrow of humans and similar cells developing in lymphoid tissue of rabbits injected with killed typhoid bacilli. The cytoplasm was described as consisting "almost entirely of fine filamentous elements lying next to one another around the nucleus". A varying number of mitochondria were observed in the cytoplasm. In animals, cells with large nuclei and nucleoli were observed soon after the injection of antigen. They showed the same lamellation of the cytoplasm described in plasma cells. When the antibody was at its peak, mature plasma cells were found, all showing the typical lamellar structure of the cytoplasm. Droplets, arising probably from the lamellar structures, were observed and were compared with similar structures described in phase microscopy.[11] Amano and Tanaka[1] demonstrated a "metamorphosis" of perivascular adventitial cells into plasma cells. Unfortunately this publication, which is in Japanese, has only a short English summary and the description of cellular detail is very sketchy.

There can be little doubt that plasma cells produce antibody, i.e. synthesize protein. In addition to experimental and immuno-histochemical evidence that plasma cells produce antibody, the electron microscope furnishes evidence that plasma cells synthesize protein. It was shown by a number of investigators[3-5, 17-20] that an endoplasmic reticulum or cytoplasmic membrane system was present only in certain cells, e.g., exocrine cells of pancreas, epithelial cells of thyroid, liver cells and pepsin-producing cells of the stomach. These cells have in common the production of a protein secretion. The cytoplasm of such cells shows intense basophilia (or pyroninophilia) in the light microscope, and contains a well-organized cytoplasmic membrane system when examined by the electron microscope. Certain other cells (myeloblasts, proerythroblasts, lymphoblasts, lymphocytes and embryonal cells) have quite an intense cytoplasmic basophilia in the light microscope, but contain no endoplasmic reticulum when examined by electron microscopy. Some cells which produce and secrete non-proteinaceous substances (e.g., steroid-secreting cells of the adrenal cortex) are neither basophilic nor do they contain endoplasmic reticulum. Therefore, it was concluded that cells which are basophilic by light microscopy and contain an endoplasmic reticulum when examined with the electron microscope, have the ability to *manufacture and secrete* protein. Thus in the electron microscope such cells contain so-called rough-surfaced vesicles, i.e., vesicles coated by RNA (ribonucleic acid) granules. There are RNA granules between the vesicles as well. Cells which are basophilic but do not produce and secrete protein (such as myeloblasts, etc.) contain smooth-surfaced vesicles (vesicles not covered by RNA granules) and have RNA granules distributed diffusely in the cytoplasm. Plasma cells belong to the first group containing both rough-surfaced vesicles and diffuse RNA granules (Fig. 6). This is indirect evidence that they synthesize and secrete protein. One is inclined to speculate that in the plasma cell the content of these vesicles is gamma globulin, which in our experiment is antibody against the injected horse serum. It is probably the same material that has been demonstrated by immuno-histochemical techniques (fluorescent microscopy).[9, 10, 16, 23] Whether these vesicles develop, perhaps under intense antigenic stimulation, into Russell bodies (in which antibody and gamma globulin have likewise been demonstrated by fluorescent microscopy) remains to be shown. It also remains to be investigated by electron microscopy from which cell the plasma cell develops upon antigenic stimulation, in both the spleen and connective tissue. It would be interesting to know also what the early changes are when a cell, presumably primitive mesenchymal, converts into a plasma cell.

## SUMMARY

The fine structure of plasma cells is described and demonstrated by means of two electron micrographs. The significance of these cells in antibody formation is discussed and correlated with the findings obtained with the electron microscope.

The authors wish to express their appreciation to Mr. Grantley Woodward, Department of Physics, University of Toronto, for invaluable assistance in the operation of the electron microscope. Grateful acknowledgment is made to Miss Charlotte Turnbull for her patience and skill in the preparation of the sections used in this study and to Mr. Harold Layne for taking the photomicrographs.

## REFERENCES

1. AMANO, S. AND TANAKA, H.: *Acta hæmat. Jap.*, **19**: 738, 1956.
2. BJORNEBOE, M. AND GORMSEN, H.: *Acta path. et microbiol. scandinav.*, **20**: 649, 1943.
3. BRAUNSTEINER, H., FELLINGER, K. AND PAKESCH, F.: *Blood*, **8**: 916, 1953.
4. BRAUNSTEINER, H. AND PAKESCH, F.: *Ibid.*, **10**: 650, 1955.
5. DALTON, A. J.: *Am. J. Anat.*, **89**: 109, 1951.
6. EHRICH, W. E., DRABKIN, D. L. AND FORMAN, C.: *J. Exper. Med.*, **90**: 157, 1949.
7. EHRICH, W. E.: *Klin. Wchnschr.*, **33**: 315, 1955.
8. FAGRAEUS, A.: *Acta med. scandinav.*, (supp. 204) **130**: 3, 1948.
9. LEDUC, E. H., COONS, A. H. AND CONNOLLY, J. M.: *J. Exper. Med.*, **120**: 61, 1955.
10. MELLORS, R. C., ORTEGA, L. G. AND HOLMAN, H. R.: *Ibid.*, **106**: 191, 1957.

11. MOESCHLIN, S., PELAEZ, J. R. AND HUGENTOBLER, F.: *Acta hæmat.*, 6: 321, 1951.
12. MORE, R. H. AND MOVAT, H. Z.: *A.M.A. Arch. Path.*, in print.
13. *Idem*: *Lab. Invest.* (G. L. Duff Memorial Issue), in print.
14. MOVAT, H. Z. AND MORE, R. H.: Morphologic evidence for the hypertensive pathogenesis of collagen disease and its experimental counterpart, *In*: First Canadian Conference on Research in Rheumatic Diseases, Toronto, Ontario, March 4, 1955. Canadian Arthritis and Rheumatism Society, Toronto, 1955, p. 65.
15. MOVAT, H. Z.: *Beitr. path. Anat.*, 116: 238, 1956.
16. ORTEGA, L. G. AND MELLORS, R. C.: *J. Exper. Med.*, 106: 627, 1957.
17. PALADE, G. E. AND PORTER, K. R.: *Ibid.*, 100: 641, 1954.
18. PALADE, G. E.: *J. Biophys. & Biochem. Cytol.*, 1: 59, 1955.
19. *Idem*: *Ibid.*, 2: 85, supp. 1956.
20. PORTER, K. R.: *J. Histochem.*, 2: 346, 1954.
21. REISS, E., MERTENS, E. AND EHRICH, W. E.: *Proc. Soc. Exper. Biol. & Med.*, 74: 732, 1950.
22. WHITE, R. G., COONS, A. H. AND CONNOLLY, J. M.: *J. Exper. Med.*, 102: 83, 1955.
23. WHITE, R. G.: *Brit. J. Exper. Path.*, 35: 365, 1954.

## RÉSUMÉ

Les auteurs de cet article ont étudié la structure fine des cellules du plasma chez le lapin après immunisation au sérum de cheval et au broyat de rein de chien. Les plasmocytes du lapin se développent à la périphérie du tissu lymphoïde, c'est-à-dire à la frontière de la pulpe rouge et de la pulpe blanche de la rate. Ces cellules possèdent un noyau excentrique à cytoplasme basophile ou pyroninophile abondant. On trouve souvent un halo juxta-nucléaire correspondant au réseau de Golgi. Les formes jeunes, plasmoblastes et pro-plasmocytes, ont un gros noyau vésiculaire et une moindre proportion de cytoplasme. La plupart des cellules sont ovales. Les auteurs ont cru reconnaître dans une substance modérément osmophile, contenue dans les vacuoles, de la globuline gamma.

On accepte maintenant la théorie de la production d'anticorps par les plasmocytes; selon la dose d'antigèneces cellules ne prolifèrent que dans la rate et les ganglions lymphatiques, ou aussi dans le tissu conjonctif autour des vaisseaux. Elles proviennent des cellules primitives du réticulum appartenant tissu hémopoïétique et des cellules primitives du mésenchyme. D'après les études expérimentales, la présence de plasmocytes en abondance laisse soupçonner une réaction d'hypersensibilité. L'intérêt de ces études tient à l'application clinique que l'on peut faire dans les affections rhumatismales et les maladies du collagène ou l'on observe souvent une augmentation des plasmocytes. Ces cellules produiraient des protéines par synthèse. Les auteurs se basent sur l'observation de basophilie, au microscope ordinaire et de reticulum endoplasmique, au microscope électronique, que l'on retrouve dans les plasmocytes comme dans les autres cellules dont la faculté de protéinosynthèse est connue depuis longtemps. Ils voient de plus dans la présence de vacuoles enduites de granules d'acide ribonucléique une confirmation de leur théorie.

---

# THE COMPARATIVE EFFECTS OF CORTICOTROPHIN (ACTH) AND STEROIDS IN HORMONAL TREATMENT

HERBERT SCHWARZ, M.R.C.S.(Eng.),
*Montreal*

THERE is a widely held impression that corticotrophin (ACTH) and steroids such as cortisone, prednisone, triamcinolone and dexamethasone are interchangeable forms of the same basic therapy. This grouping together of corticotrophin with steroids obscures the very vital differences between the results of stimulation therapy on one hand and substitution on the other.

Although newer, more potent steroids are continually being introduced, they all retain the major cortisone drawback of suppressing adrenal cortical activity, even after short-term administration. When used for a long time, steroids cause complete atrophy of the adrenal cortex to the point where the outcome may be fatal, as for example in severe stress when the demand for adrenal hormones is greatly increased. In this respect, the continuous use of steroids without pauses for courses of ACTH stimulation has been described as "medical adrenalectomy".

The onset of adrenal atrophy is gradual, with no warning symptoms, under the cover of the substituted hormone. It is dangerous because an acute episode of stress, such as an infection or accidental injury, may occur without sufficient adrenal reserve to meet it. The literature reports a number of such incidents in which even minor trauma led to a fatal outcome in patients on small maintenance doses of corticoids or after cessation of treatment.

Unlike the steroids, ACTH stimulates the adrenal cortex and hence atrophy of this gland is no problem. Although exogenous ACTH replaces that normally produced by the pituitary, this suppression is of short duration even after long-term administration. Indeed, when ACTH is withdrawn, the adrenal cortex is usually hypertrophic and it will still respond to normal amounts of ACTH. For this reason, the severe rebound phenomena associated with sudden withdrawal of steroids are rarely seen when ACTH is discontinued.

Apart from this difference in effect on adrenal function, ACTH appears to influence metabolic processes in a manner that differs qualitatively as well. Some of these metabolic actions may result from the "extra-adrenal" effects of ACTH, while others may represent the action of the non-cortisone sections of the "steroidal spectrum" that results from ACTH stimulation.

It is our purpose to review the considerable body of literature that has accumulated on these differences between the cortisone steroids and ACTH, and to present several cases illustrating the point that an awareness of these data, both experimental and clinical, may lead to a more balanced approach to corticotrophin-steroid therapy.

## RISK OF ADRENAL ATROPHY—IS IT REAL?

Long before the clinical use of cortisone, atrophy of the adrenal cortex had been observed in animals

Canad. M. A. J.
Aug. 1, 1959, vol. 81

after adrenal extract administration, as had its hypertrophy after corticotrophin.[1, 2]

With the advent of oral, easily administered steroids and their dramatic impact in a variety of diseases, the equally effective action of ACTH was overshadowed largely for the sake of convenience. Only gradually did an awareness of the fact that adrenal atrophy may complicate steroid treatment develop, and even then, adrenal inhibitory effects were sometimes ascribed to ACTH, although clinical evidence of such effects has not been produced. On the contrary, pathological examinations have shown that the effects of these hormones on human adrenals are similar to those seen in the experimental animals.[3-7] Lewis *et al.*[9] have summarized much of what has been written on this point by the following comment: "Withdrawal of ACTH seldom leads to the prompt relapses in disease and quasi-addisonian state induced by sudden cessation of oral cortisone treatment, possibly because the increased responsiveness of the patient's adrenals partly compensates for lessened pituitary ACTH output".

Stoner and Whiteley[7] were able to compare the weight and functional status of adrenal glands removed at autopsy from patients treated for varying periods with either ACTH or cortisone. The glands from the ACTH-treated cases were enlarged and had been active up to the time of death, while the adrenals of the cortisone-treated patients were atrophic and inactive. Their findings are summarized by drawing attention to the possibility that "a situation can be created by the use of cortisone which will greatly impair the efficiency of the body in dealing with further assault. For these reasons, corticotrophin seems to be preferable to cortisone . . ."

Myers and Wolfson,[8] commenting on this same problem as it faces the clinician, state: "When a long-term regimen is indicated, corticotrophin is vastly preferable because it maintains the adrenals in a hyper-responsive state so that therapy enables the patient to weather the minor stresses of everyday life and prepares him to withstand the major stress of serious injury or surgery . . . After hydrocortisone or cortisone has been given on a long-term basis, marked adrenal atrophy occurs and adrenal unresponsiveness may persist for weeks or months . . . which may be unrecognized until an emergency, when even a minor stress may precipitate acute adrenal insufficiency." These authors recommend giving all patients from whom cortisone is being withdrawn, 100-unit doses of long-acting ACTH for three successive days, or weekly injections of 100-200 units of ACTH when the oral steroids are given as long-term treatment.

Arlotti[33] describes a "steroid withdrawal syndrome" after courses of prednisone, characterized chiefly by weakness, nausea and depression, which can be prevented by the simultaneous administration of small doses of long-acting ACTH. Vermeulen[34] examined the persistence of adrenocortical inactivity after cessation of treatment with prednisone and prednisolone, and found it necessary to administer a combination of ACTH and prednisone for five to seven days, and ACTH alone for three days, at the end of each treatment with the oral steroids in order to lower the risks of hypocorticism within reasonable limits.

Although depression of the adrenal cortex is generally considered to be always reversible, Kanee and Mallek[37] have recently described the case of a patient treated with prednisone, whose adrenals show a complete failure to produce endogenous hormone and are no longer responsive to repeated and continuous ACTH stimulation. This patient with neurodermatitis disseminata responded well to ACTH at first. After six months on prednisone, no effect on the eosinophil count was noted after daily 8-hour intravenous ACTH drip for five days. After continuing for a further six months on prednisone, the patient suffered an addisonian-like collapse during the added stress of a respiratory infection. Intravenous hydrocortisone combined with antibiotics effected a recovery. Some months later, a further attempt to stimulate adrenocortical function, this time with intravenous ACTH for a week, again proved unsuccessful. The patient has subsequently required continuous maintenance with prednisone, and an attempt to discontinue therapy has demonstrated complete inadequacy of the patient's own adrenocortical system.

There is general agreement that any stress situation occurring during or after steroid therapy, such as infection, injury or surgical procedures, requires additional steroid during the emergency to compensate for the inactivity of the suppressed gland.[5-7, 9, 12a] In the case cited above[37] an infection led to profound collapse and the patient was saved only by the prompt infusion of hydrocortisone. Thus, if severe stress occurs within six months after discontinuance of steroid therapy, the patient must be given adequate amounts of steroids intravenously and orally, as long as the stress continues, to prevent adrenal insufficiency and collapse. The preoperative use of intravenous ACTH in cases of stress not previously treated with steroids, and also postoperatively, has been suggested.[5, 8, 9]

### COMPARATIVE EFFECTS OF VARIOUS STEROIDS ON ADRENOCORTICAL FUNCTION

While the newer steroids have greater anti-inflammatory potency than cortisone, their suppressive effect on the adrenal cortex is likewise enhanced. As a rule the anti-inflammatory activity of a corticoid is in proportion to its pituitary corticotrophin and adrenal-suppressing activity. Kupperman[10] examined the suppressive effect of various steroids on excessive 17-ketosteroid secretion in the adrenogenital syndrome. He lists suppressive potency in the order: 9 alpha-fluorohydrocortisone, prednisone, hydrocortisone, cortisone, the latter being least suppressive on a weight

basis. Done, Ely and Kelley[11] compared adrenocortical responsiveness in rheumatic fever patients after treatment with salicylates, cortisone, ACTH or bed rest alone. Plasma 17(OH)-corticosteroid levels were determined in response to intramuscular ACTH before and after treatment. The tests showed that adrenal response was greatly decreased after both salicylate and cortisone therapy and near pre-treatment levels after therapy by ACTH and bed rest. Christy *et al.*,[12] in comparing the effects of cortisone and prednisone, noted that the latter was at least four times as effective as cortisone in suppressing the adrenocortical response to exogenous ACTH, and that adrenal hypofunction occurred after only seven days of prednisone on a dosage of 25 mg. per day. These authors suggest that normal adrenal responsiveness may be restored by corticotrophin treatment, although they stress that this does not imply restoration of full pituitary reactivity in stress situations.

### COMBINED TREATMENT—STEROIDS PLUS ACTH

In order to combine the advantage of oral steroids with the greater safety of injected ACTH, various attempts have been made to combine the two in maintaining the functional integrity of the adrenal cortex.[3, 8, 13, 14, 33, 35] With the advent of satisfactory preparations of long-acting ACTH, such programs have become feasible.

Birke *et al.*,[13] after noting that only seven days of treatment with a daily dose of 30 mg. of prednisone was sufficient to cause almost complete disappearance of adrenal steroid secretion, concluded that it would be advisable to administer ACTH intermittently during prolonged steroid treatment and suggested an injection every seventh or tenth day.

The dosage of ACTH recommended by Birke and his group corresponds to 30 i.u. of the long-acting ACTH units employed in North America. Young and his collaborators,[14] however, found that at least 200 units was required in a weekly injection to maintain adrenal responsiveness and that once the adrenal had been suppressed a single injection was not sufficient. These dosage variations between the Swedish and the American group may be explained partly by the differences in the criteria used to evaluate adrenal function, and partly by differences in the long-acting ACTH used by the two groups.

In Canada, the author has used a weekly injection of 40 to 80 i.u. of a long-acting preparation* in patients receiving long-term steroid treatment, the dosage depending upon the amount and kind of steroid given. In any stress situation, it would seem advisable to increase the steroid dose temporarily; in withdrawing steroids, ACTH should be used in a daily injection until adrenocortical reactivity has definitely been restored.

*Duracton (Nordic Biochemicals Ltd.).

### PHYSIOLOGICAL DIFFERENCES AND CLINICAL EFFECT

There is considerable evidence from both experimental and clinical work[15-19, 27] that qualitative differences exist between the metabolic actions of the cortisone-like steroids and ACTH. Some of these differences have been described as "extra-adrenal" effects of ACTH, and others are attributed to the action of ACTH-stimulated adrenal steroids other than cortisone.

Corticosteroid therapy is considered to have a catabolic (or anti-anabolic) effect in animals and humans. This may serve to explain its reported effect in delaying wound healing and in breaking down natural barriers to infections such as tuberculosis. It has been shown by Selye,[15] however, that in the rat, ACTH can suppress inflammation at a dose level which does not cause any significant catabolism, whereas the dose of hydrocortisone required to reverse the same degrees of inflammation has a pronounced catabolic effect. LeMaistre and Tompsett[17] found that ACTH had a less deleterious effect on experimental tuberculosis than did cortisone. This was confirmed by Morgan, Wanger and Smith[19] in the rabbit. On the basis of these results, Grégoire[20] has shown that ACTH, when used together with antibiotics, may be used safely (and successfully) in the treatment of patients with tuberculous asthma. Des Pres and Organick[32] administered ACTH and cortisone as supportive treatment in selected patients with tuberculosis, and their data suggest more favourable results with the former.

Hills, Zintel and Parsons[30] have shown in adrenalectomized patients that cortisone does not provide complete replacement for the missing adrenal cortical secretions and that such factors as melanosis, impaired water diuresis, unresponsiveness to hypoglycæmia, azotæmia and hyperkalæmia are not controlled by the single steroid. This suggests the existence of other adrenal substances having functions additional to those of cortisone (or more correctly, hydrocortisone), which may be necessary in a complementary or synergistic way. Hechter and Pincus[31] have reviewed the other physiologically active adrenal cortical hormones. The production of these additional hormones under ACTH stimulation may explain why a number of diseases respond more completely to ACTH than to cortisone therapy.

In a recent paper on multiple sclerosis, Alexander *et al.*[21] have found ACTH to be effective in reversing some forms of this disease, while cortisone and prednisone were without comparable benefit. The authors comment on this observation that "This seems to indicate that the adrenal hormones responsible for improvement under the stimulating effect of corticotrophin may be hormones in addition to or other than cortisone."

Various diseases respond to treatment with both ACTH and the steroids, but in some the former appears to be more effective. Thus Pillsbury and

Canad. M. A. J.
Aug. 1, 1959, vol. 81

Urbach found cortisone less effective than ACTH in pemphigus.[28] The same conclusions in ulcerative colitis were drawn by Kirsner and Palmer[29] and in certain blood dyscrasias by others.

### RHEUMATOID ARTHRITIS AND HORMONAL TREATMENT

In the arthritic diseases, there is a growing body of data indicating that ACTH may have a more profound effect in arresting the disease than is the case with any cortisone-like steroid developed to date. Since both types of therapy offer such marked subjective improvement, these differences appear only after long-term treatment. West and Newns[22] compared two groups of patients, one on long-term ACTH and the other on cortisone. The ACTH group fared considerably better both objectively and subjectively; this was particularly emphasized by the radiological examinations showing that bony erosions of the arthritic process had been arrested in 81% of the ACTH-treated group, while evidence of continued erosion was present in almost 60% of the cortisone-treated group.

In an extension of these studies, West[23] confirms these findings in additional patients and notes in summary ". . . that adrenocortical stimulation therapy, providing a daily urinary output of from 20 to 30 mg. 17 (OH)-CS favourably affects the course of severe rheumatoid arthritis over prolonged periods in the majority of patients, and that in this respect it is superior to oral cortisone therapy." He also notes the freedom from serious side effects, including the absence of peptic ulceration, when the ACTH dosage is kept within moderate limits.

Jordal,[24] summarizing his experience in 45 patients with rheumatoid arthritis and three with rheumatoid spondylitis, notes: "A comparison has been made between cortisone and corticotrophin therapy, and it is given as our opinion that the latter drug should be preferred for long-term therapy . . ." Here, again, the author urges the use of the smallest possible dose of ACTH and ascribes much of the success of long-term treatment to the avoidance of the larger, more dramatic dosages.

Savage and his colleagues[25] reported on 75 patients with severe active rheumatoid arthritis, some of whom were given long-term ACTH after failure to respond to other forms of treatment. They note that with ACTH there was a higher rate of remissions than after similar periods of oral steroids and also note that the distressing withdrawal symptoms usually seen with cortisone were absent with ACTH.

In the later report from the same group[26] it is noted that ACTH control of rheumatoid arthritis can be adjusted much more closely than with cortisone, when measurement of urinary 17-hydroxycorticosteroids is used as the criterion of adrenal stimulation. This enables therapy to progress with a minimum incidence of side effects. Thus, the authors note that out of 49 patients followed up for at least six months, only one developed peptic ulceration while being given ACTH, whereas 13 out of 83 consecutive patients treated with steroids developed gastric or duodenal ulceration.

Commenting on the reports to date on steroid and ACTH therapy of arthritis, an editorial in the *British Medical Journal*[27] outlines the disadvantages of oral steroids and the alarmingly high incidence of side effects. While holding that the results of prolonged ACTH therapy appear to be more promising, it urges continued efforts to produce ACTH preparations of greater uniformity and purity in order to explore further the advantages of the latter treatment.

In agreement with most of the reviews cited above, the author has obtained the best results in rheumatoid arthritis when the ACTH dosage has been kept low from the outset. It is also our experience that too complete suppression of symptoms may encourage excessive physical activity while the disease process is still present. Patients should receive only enough of the hormone to lessen some of the swelling and relieve pain to the point where remedial and supportive treatment may proceed.

### A PRACTICAL APPROACH TO LONG-TERM ACTH TREATMENT

While the advantage of oral administration weighs heavily in favour of the steroids, the above considerations have led us to seek methods for the administration of ACTH on a basis that can be used for non-hospitalized patients. The aim has been to arrive at a method of response estimation that will eliminate the need for continual laboratory procedures and at the same time avoid the consequences of overdosage.

In earlier days, the use of multiple daily injections resulted in cumulative overdosage effects. Although the initial result was a dramatic symptomatic improvement, this method was obviously ill suited to long-term treatment even in hospitalized patients. Intravenous ACTH offered better control, but again, was obviously only a hospital procedure.

The appearance of long-acting ACTH preparations made possible the treatment of patients as an office procedure. The early preparations were recommended only for intramuscular injection, and therefore efforts were made to keep the frequency of the injections to a minimum. In most patients it was possible to give an injection every two or three days, but the dosage required to provide continuous adrenal stimulation during this interval was, in the light of later experience, excessively high and carried with it an incidence of side effects that was due entirely to overdosage.

Since the demonstration by Fyles and Rose[36] that long-acting ACTH may be administered subcutaneously, it has become possible to teach many patients self-administration. Thus, it has been our experience that a daily injection combines the advantages of extremely low doses with a routine

that is acceptable and economical to most patients. By carefully instructing patients in the nature of overdosage and side effects, and by following the clinical course especially closely during the first few weeks of therapy, it is possible to arrive at a dosage level just sufficient to suppress the undesirable symptoms without giving rise to untoward effects. While the required dosage may vary from time to time, both the physician and the patient learn to recognize such variations and compensate accordingly.

In a four-year period, the author has treated 43 cases of a variety of diseases with ACTH, for varying lengths of time. In no single instance did serious side effects develop. An occasional case of fluid retention has been controlled by dosage reduction without requiring cessation of therapy.

Several of these cases will illustrate the long-term course of patients whose condition has been managed in the manner suggested above.

CASE 1.—This 60-year-old woman, suffering from a mixed osteoarthritis and rheumatoid arthritis, had been treated with cortisone for one year, the average daily dose being 50 mg. per day. On this regimen, she had obtained only partial relief from symptoms and still complained of pain and joint stiffness.

After a year of cortisone medication, the patient developed a spontaneous fracture of the 10th thoracic vertebra, which was attributed to steroid therapy, and the latter was abruptly discontinued.

When first seen a year later, the patient was bedridden with inflamed, painful and stiffened joints, and complained of a severe backache. ACTH (Duracton) therapy began in doses of 80 i.u. daily for eight days and this was gradually reduced to 10-15 i.u. daily, administered by the patient's daughter. To begin with, the patient was seen once a week, and her general condition and response to ACTH evaluated; later, with smaller doses, her condition was checked only once a month. On the Duracton regimen, the patient improved in a remarkable manner. She is free from pain, her joint swelling has subsided and she is able to do a limited amount of walking.

The patient continued with Duracton 10-15 i.u. daily for the last three years, all administered at home.

The only side effect is an occasional peripheral swelling, kept under control with oral diuretics and temporary reduction in ACTH dosage. Radiologically, there has been no progression of osteoporosis in the last three years, and her blood pressure has not changed.

CASE 2.—This 45-year-old farmer, suffering from rheumatoid arthritis, was treated with prednisone for three months. On the average, he took 10-15 mg. of steroid per day and on this regimen he obtained only poor control of symptoms and lost 15 lb. in weight. Eventually, prednisone was stopped because of indigestion and flatulence, and ACTH therapy was begun.

For the first month, the patient required 40 i.u. of ACTH (Duracton) daily, which he was taught to administer to himself. He was supervised once a week in the office, and his subjective and objective symptoms were evaluated. There was marked clinical improvement in his general condition; he regained weight, was free of pain and was able to engage in moderate physical activities.

The dose of ACTH was gradually tapered to 10-15 i.u. daily. This is enough to control most of the joint symptoms, and it keeps him free of pain. The dosage is not large enough to obscure his rheumatic condition entirely, as it was found that with larger amounts of ACTH the patient had a false feeling of security and tended to over-exert himself.

CASE 3.—This man of 28 came for advice because of recurrent hay fever and bronchial asthma. He had recently been treated with prednisone 15-25 mg. daily for two weeks and on this dosage he had obtained some relief from symptoms. Because of digestive disturbances, prednisone was discontinued. Two days later, the patient's hay fever recurred in a very severe form and he was greatly troubled with nocturnal bronchial asthma. He was put on ACTH (Duracton) 40 i.u. per day for three days but with no result. The dose was increased to 60 i.u. per day for three days, and then to 80 i.u. daily for another four days, still with no clinical improvement.

As the tests undertaken with the ACTH used revealed no decrease in potency, it was felt that we were dealing with adrenal unresponsiveness following steroid therapy. When seen again in two weeks he was acutely ill and once more he was tried with ACTH (Duracton) 40 i.u. per day and he obtained almost immediate relief from symptoms. After a few days the dose was tapered to 10-15 i.u. per day and the patient was taught to administer his own injections.

With periodic check-ups the patient was able to control his manifestations with daily dosage of 10-15 i.u. subcutaneously. This was continued till the end of the hay fever season, and the ACTH administration was gradually tapered off and then stopped.

CASE 4.—This woman of 28 developed an acute rheumatoid arthritis which was treated with cortisone and later hydrocortisone with excellent results.

However, after several months of treatment, the patient required increasingly higher doses of hydrocortisone to suppress her arthritic phenomena, and eventually it was discontinued.

It was felt that after prolonged steroid administration, the patient's need for ACTH would be higher. She was put on 80 i.u. per day for two weeks to allow for adrenal recovery, and the dose was gradually reduced to 10 i.u. per day. The patient did extremely well, joint pains and swelling largely subsided and she was able to engage fully in her household tasks.

During that time she was taught to administer her own ACTH, with small dosage adjustments during intercurrent infections or periods of mental stress. She was instructed at all times to report any unusual phenomena while under treatment, and her condition was checked once a month in the office.

In the third year of therapy the patient went into complete remission and it was possible to taper off ACTH and then discontinue it entirely.

CASE 5.—This woman of 52 developed an acute attack of disseminated lupus erythematosus and was admitted to hospital. Hydrocortisone was administered in large doses of 1-3 g. per day. There was no significant improvement after several months of this treatment.

She was sent home and continued with massive doses of hydrocortisone. There was gradual deterioration of the patient's condition while at home; she lost weight and, in addition to her joint and skin changes, developed dry pleurisy and pericarditis. Eventually hydrocortisone was discontinued and ACTH (Duracton) therapy begun, first with relatively large doses of 80 i.u. daily. As gradual improvement began, this was tapered to 15-25 i.u. daily. The hormone was administered to the patient by her husband. Within the allowed range of 15-25 i.u. per day, the dose was regulated according to the patient's needs.

Although still very ill, in the first year of ACTH therapy the patient gained weight, and the pleural and myocardial rubs disappeared.

Altogether the patient continued for a period of four years on long-acting ACTH administered by the husband, with regular medical check-ups at home.

Lately she has gone into partial remission and requires only minimal doses — 5-10 i.u. every second or third day.*

## SUMMARY AND CONCLUSIONS

A review of the literature reveals that there are important qualitative differences in the modes of action of ACTH and of cortisone and its analogues. ACTH does not cause atrophy of the adrenal cortex, and the distressing withdrawal symptoms associated with the oral steroids are less frequently encountered. ACTH appears to be less catabolic than the oral steroids in therapeutic dosages. ACTH appears to influence favourably a number of diseases incompletely controlled by the oral steroids. Some of the undesirable effects of oral steroids, such as adrenal atrophy, may be avoided by combining them with intermittent administration of ACTH.

A regimen of long-term ACTH therapy is suggested on a basis of sound co-operation between patient and physician, which should lead to the early recognition of side effects due to overdosage. It is suggested that daily injection of long-acting ACTH at levels just sufficient to suppress disease symptoms constitutes a safe course of treatment that may be continued indefinitely.

The need for careful screening of patients before instituting any form of adrenocorticosteroid therapy should be emphasized and these hormones should be used only after conservative measures have been thoroughly explored.

The author is grateful to the firm of Nordic Biochemicals Ltd., Montreal, for part of the supplies of Duracton used in some of these cases.

### REFERENCES

1. INGLE, D. J. AND HIGGINS, G. M.: *Am. J. M. Sc.*, **196**: 232, 1938.
2. WELLS, B. B. AND KENDALL, E. C.: *Proc. Staff Meet. Mayo Clinic*, **15**: 324, 1940.
3. COLLINS, E. J. AND OLSON, K. J.: *Proc. Soc. Exper. Biol. & Med.*, **87**: 76, 1954.
4. SOKOLOFF, L., SHARP, J. T. AND KAUFMAN, E. H.: *Am. J. Path.*, **27**: 706, 1951 (abstract)
5. FRASER, C. G., PREUSS, F. S. AND BIGFORD, W. D.: *J. A. M. A.*, **149**: 1542, 1952.
6. SALASSA, R. M. *et al.*: *Ibid.*, **152**: 1509, 1953.
7. STONER, H. B. AND WHITELEY, H. J.: *Lancet*, **2**: 992, 1954.
8. MYERS, G. B. AND WOLFSON, W. Q.: Corticotropin, its pharmacologic effects in man and practical therapeutic utilization, Wayne State University Press, Detroit, 1955, p. 7.
9. LEWIS, L. *et al.*: *Ann. Int. Med.*, **39**: 116, 1953.
10. KUPPERMAN, H. S. *et al.*: *J. Clin. Endocrinol.*, **15**: 911, 1955.
11. DONE, A. K., ELY, R. S. AND KELLEY, V. C.: *Metabolism*, **7**: 52, 1958.
12. CHRISTY, N. P., WALLACE, E. Z. AND JAILER, J. W.: *J. Clin. Endocrinol.*, **16**: 1059, 1956.

12a. Editorial: *J. A. M. A.*, **148**: 1422, 1952.

13. BIRKE, G. *et al.*: *Acta med. scandinav.*, **155**: 245, 1956.
14. YOUNG, I. I. *et al.*: *A.M.A. Arch. Int. Med.*, **100**: 1, 1957.
15. SELYE, H.: *Metabolism*, **4**: 403, 1955.
16. BACOS, J. M. AND SMITH, D. T.: *Am. Rev. Tuberc.*, **67**: 201, 1953.
17. LE MAISTRE, C. AND TOMPSETT, R.: *Ibid.*, **64**: 295, 1951.
18. *Idem*: *J. Exper. Med.*, **95**: 393, 1952.
19. MORGAN, T. E., WANGER, S. H. AND SMITH, D. T.: *J. Bact.*, **67**: 257, 1954.
20. GRÉGOIRE, F.: *Canad. M. A. J.*, **74**: 146, 1956.
21. ALEXANDER, L., BERKELEY, A. W. AND ALEXANDER, A. M.: *J. A. M. A.*, **166**: 1943, 1958.
22. WEST, H. F. AND NEWNS, G. R.: *Lancet*, **1**: 578, 1955.
23. WEST, H. F.: *Ann. Rheumat. Dis.*, **16**: 322, 1957.
24. JORDAL, R.: *Danish M. Bull.*, **3**: 24, 1956.
25. SAVAGE, O. *et al.*: Clinical and biochemical study of rheumatoid arthritis during treatment with corticotrophin, paper presented at the Ninth International Congress on Rheumatic Diseases, Toronto, June 23-28, 1957.
26. *Idem*: *Brit. M. J.*, **2**: 1257, 1957.
27. Editorial: *Ibid.*, **2**: 1291, 1957.
28. PILLSBURY, D. M. AND URBACH, F.: Diseases affecting the skin, *In*: Medical uses of cortisone, edited by F. D. W. Lukens, The Blakiston Company, Inc., New York, 1954, p. 364.
29. KIRSNER, J. B. AND PALMER, W. L.: *Ann. Int. Med.*, **41**: 232, 1954.
30. HILLS, A. G., ZINTEL, H. A. AND PARSONS, D. W.: *Am. J. Med.*, **21**: 358, 1956.
31. HECHTER, O. AND PINCUS, G.: *Physiol. Rev.*, **34**: 459, 1954.
32. DES PRES, R. M. AND ORGANICK, A.: *A.M.A. Arch. Int. Med.*, **101**: 1129, 1958.
33. ARLOTTI, O.: *Minerva med.*, **48**: 4143, 1957, abstracted *In*: *J. A. M. A.*, **167**: 388, 1958.
34. VERMEULEN, A.: *Acta endocrinol.*, **28**: 321, 1958.
35. VACCARI, F. AND ONESTI, G.: *Minerva med.*, **48**: 2959, 1957.
36. FYLES, T. W. AND ROSE, B.: *Canad. M. A. J.*, **70**: 551, 1954.
37. KANEE, B. AND MALLEK, J.: *Ibid.*, **79**: 468, 1958.

6743 Fielding Ave.,
Montreal, Quebec.

*In some of the above cases, treatment was started before June 1956, after which the method of expressing ACTH potency was changed. All dosages have been recalculated in terms of the units presently in use in Canada.

## RÉSUMÉ

Une synthèse de la documentation relative à l'ACTH et à la cortisone et ses analogues, montre qu'il existe des différences qualitatives importantes dans leur mode d'action. L'ACTH ne produit pas d'atrophie corticosurrénalienne et les pénibles symptômes de sevrage observés après l'interruption des stéroïdes oraux ne se présentent pas aussi fréquemment. A doses thérapeutiques l'effet catabolique de l'ACTH semble moindre. L'ACTH paraît influencer favorablement un nombre de maladies qui échappent en partie au contrôle des stéroïdes. Il semble donc sage de combiner les deux médicaments pour mieux équilibrer la thérapie.

L'auteur préconise l'emploi d'ACTH-retard dans les traitements à longue échéance. Il prétend qu'une posologie visant uniquement à supprimer les symptômes est inoffensive et peut être maintenue indéfiniment. Il insiste cependant sur un choix judicieux des malades et ne recommande qu'on ait recours à cette forme de traitement que lorsque les moyens plus conservateurs ont été épuisés.

---

## SURGICAL PAROTITIS

Postoperative parotitis usually occurs in a seriously ill, dehydrated, undernourished patient with poor oral hygiene. Resistant *Staphylococcus aureus* infections in a hospital lead to more parotitis as a complication. It occurs after a four- to six-day period of restricted oral intake of fluid, and oral hygiene should be particularly stressed during this period in those seriously ill from inflammatory conditions. X-ray therapy is recommended as soon as the diagnosis is made. If symptoms progress, surgical incision and splitting of the parotid capsule under procaine anæsthesia is recommended.

The demonstration of fluctuation in the parotid gland is difficult and leads to delay in treatment which may be serious.—R. K. Gilchrist and J. R. McAndrew: *A.M.A. Arch. Surg.*, 76: 863, 1958.

# GRISEOFULVIN IN THE ORAL TREATMENT OF TINEA CAPITIS*

A. R. BIRT, M.D.,† J. HOOGSTRATEN, M.D., Ph.D.‡ and M. NORRIS, M.S.,¶ *Winnipeg, Man.*

A KNOWLEDGE of the pathogenesis of tinea capitis is necessary to understand the difficulties encountered in treating this troublesome disease. The dermatophytes which cause tinea capitis possess the rare property of being able to invade and exist on keratin. When they try to invade other tissues they cause a reaction and are thrown off. Kligman[1] recently amplified Sabouraud's[2] original observations regarding the method of invasion of the hair by fungi. Initially the spores become lodged in the follicular openings where they germinate to produce a mass of fungal filaments that entwine the hair. They then grow down on the hair before they invade it about half way down the follicle, and continue to grow down in the hair until they reach the keratogenous zone of the hair matrix. The keratogenous zone is the viable area where keratin is formed, and the fungi cannot invade it. It corresponds to Adamson's fringe. The fungi are then carried outwards by the hair growth. As they multiply in the hairs, the keratin becomes disorganized and the hairs break off. Thus the active site of infection in tinea capitis is deep in the hair follicle, and so far has been beyond the action of locally applied antifungal agents.

Wilson[3] anticipated the advent of oral therapy for superficial mycotic infections when he said, "The ideal antifungal drug even for superficial mycoses would seem to be one which could be safely administered internally in amounts sufficient to endow the cells eventually destined to produce keratin with the power to resist fungi completely, this power persisting as they become keratinized, and the drug thus exerting its effects from within outward." Gentles[4] thought that griseofulvin might answer these criteria, and used the drug successfully in the oral treatment of guinea pigs experimentally infected with *Microsporum canis* and *Trichophyton mentagrophytes.*

Recently Williams, Marten and Sakarny[5] reported using griseofulvin in the treatment of human subjects suffering from chronic fungous infections. Nine patients with *Trichophyton rubrum* infections of the skin and nails were treated, and one patient with *Microsporum audouini* infection of the scalp. All responded favourably. This report was significant enough to merit an editorial in the *Lancet,* and to stimulate the interest of all faced with the problem of treating superficial fungous infections in humans.

Griseofulvin is an antibiotic with antifungal properties. It was isolated by Oxford *et al.*[6] in 1939 from *Penicillium griseofulvum dierckx.* It has been shown to have a very low acute toxicity when administered orally to animals in very large doses. However, Paget and Walpole[7] have noted a colchicine-like effect on mitosis when the drug was given intraperitoneally or intravenously in very large doses to experimental animals. Griseofulvin is absorbed and excreted rapidly. The dosage for human patients has not been completely established. It has been suggested that one gram be given daily as a single dose or in divided doses. Griseofulvin is supplied in 250-mg. tablets.

Since December 1958, seven boys with superficial fungous infections have been treated by oral administration of griseofulvin at the Children's Hospital of Winnipeg. There were four brothers with tinea capitis due to *M. canis;* one boy with tinea corporis due to *T. mentagrophytes;* and two brothers with *M. audouini* infection of the scalp. The first five children were admitted to hospital for the duration of their treatment, and the other two were observed twice weekly in the outpatient department. Because griseofulvin is still experimental in human subjects, the children were submitted to a battery of tests during the course of therapy. The tests, done at three-day intervals, included complete blood counts and urinalyses; determinations of total and direct bilirubin; thymol turbidity and cephalin cholesterol flocculation tests; bromsulfalein retention tests; blood urea nitrogen and alkaline phosphatase determinations. At no time during the course of treatment did the results of any of these tests deviate from normal. There was no weight loss and the boys appeared to be quite healthy. Except for a daily shampoo with spirts of green soap, no local therapy was used.

## CASE REPORTS

CASE 1.—This 13-year-old, 93-lb. boy had a few hairs which fluoresced under Wood's light in an oval patch at the top of his head. There was no clinical evidence of infection. He was started on griseofulvin, 250 mg. twice daily. Five days later a typical clinical lesion of tinea capitis had developed with short broken lustreless hairs and bright green fluorescence. *M. canis* was found on culture. Twelve days from the time of onset the scalp in the affected area was erythematous, but there was no evidence of follicular pustular response. At the end of 21 days the fluorescence had disappeared and only a fine scaling was left.

CASE 2.—An 11-year-old, 80-lb. boy had two areas of tinea capitis over the occipital region of the scalp of two weeks' duration. There was partial alopecia, lustreless broken hairs, erythema and a fine scaling over the affected area of the scalp, and bright green fluorescence under Wood's light. *M. canis* was found on culture. He was treated with griseofulvin, 250 mg. twice daily. After one week there was some evidence

---

*This work was done at the Winnipeg Children's Hospital with the kind co-operation of H. Medovy, M.D., pædiatrician in chief, S. Israels, M.D., associate professor of pædiatrics, and A. Zipursky, M.D., lecturer and research worker in pædiatrics.
†Assistant Professor of Medicine (Dermatology), University of Manitoba.
‡Assistant Professor of Pathology, University of Manitoba.
¶Special Demonstrator in Bacteriology, University of Manitoba.
The griseofulvin was supplied by Glaxo-Allenburys (Canada) Limited.

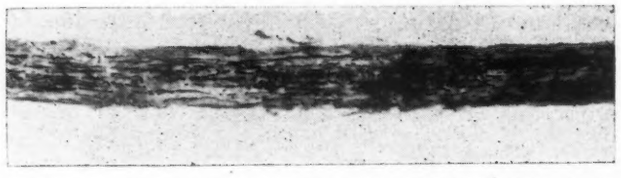


Fig. 1.—Hair infected by *M. canis*. Modified Gram stain, × 160.

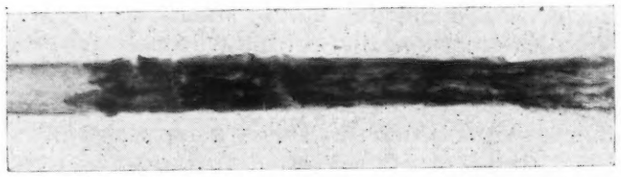


Fig. 2.—Infected hair showing the disappearance of spores at the proximal end after the oral administration of griseofulvin. Modified Gram stain, × 100.

of follicular reaction with the development of small follicular crusts. This subsided quickly and the fluorescent hairs started to fade. He was judged to be cured at the end of 21 days of treatment.

CASE 3.—A nine-year-old, 60-lb. boy had an area of tinea capitis in the left parietal region and another over the vertex, of two weeks' duration. There was considerable erythematous reaction in the affected areas of the scalp, and the hairs were bright green under Wood's light. *M. canis* was found on culture. He was treated with griseofulvin, 250 mg. twice daily. In spite of therapy the reaction in the scalp progressed, follicular pustules appeared and a typical kerion developed. After three weeks' therapy it was noted that the fluorescence was disappearing from the hairs close to the scalp but remained in the distal portion of the hairs. The kerion ran the typical course seen with *M. canis* infection in Manitoba, and the lesion was not completely cured until 60 days of treatment had elapsed, or 2½ months from the first appearance of the infection.

CASE 4.—A four-year-old, 40-lb. boy had an oval lesion of tinea capitis over his occipital region, and small scattered lesions over the rest of his scalp, of four weeks' duration. Some follicular pustules were present, and the hairs fluoresced bright green under Wood's light. *M. canis* was grown on culture. He was treated with griseofulvin, 250 mg. twice daily. After 18 days the fluorescence of the hairs began to fade at the level of the scalp, but the follicular pustules responded very slowly. There was no evidence of the disease after 32 days' treatment. This was two months after the onset of the disease.

CASE 5.—A 12-year-old, 80-lb. boy had tinea corporis on his right forearm due to *T. mentagrophytes*. The lesion was oval and erythematous, and contained vesico-pustules. It had been present for about two weeks and had been painted with iodine on three or four occasions before he was brought into the clinic. Griseofulvin, 250 mg. twice daily, was prescribed. Pustules continued to develop during the next ten days. The lesion appeared to run a normal course and disappeared after 26 days' treatment, or six weeks from the onset of the disease.

CASE 6.—A six-year-old, 57-lb. boy had tinea capitis due to *M. audouini*. The lesion was an oval area in the left parietal region and it fluoresced brightly under Wood's light. It had been present for two months before the start of griseofulvin therapy. He was given griseofulvin, 250 mg. four times daily. Within two weeks the fluorescence was disappearing at the scalp level. The hairs were not cut. Gradually the fluorescence cleared, always from the scalp level, until there were just tiny green tips left at the periphery of the lesion. The hairs were clipped after 40 days of therapy. There has been no further evidence of the disease after a one-month follow-up.

CASE 7.—A four-year-old, 40-lb. boy had an area of tinea capitis due to *M. audouini* in the left parietal region. The lesion had been present for one month before the starting of therapy, and the hairs fluoresced bright green under Wood's light. He was treated with griseofulvin, 250 mg. four times daily. Within two weeks the fluorescence started to fade at scalp level. After 40 days there were just tiny green fluorescent tips left on the hairs at the periphery of the lesion. These hairs were clipped off and there has been no further evidence of the disease.

## DISCUSSION

Griseofulvin, given by mouth, apparently marks a major advance in the therapy of tinea capitis due to *M. audouini*. In Cases 6 and 7, the fluorescence disappeared first at scalp level and then gradually grew out with the hairs until only tiny fluorescent tips were left at the distal ends of the most recently infected hairs at the periphery of the lesions. Gentles also observed this phenomenon in guinea pigs experimentally infected with *M. canis*. This observation was confirmed microscopically. Fig. 1 shows a section of hair infected with *M. canis*. Fig. 2 shows a similar hair after griseofulvin therapy. In Fig. 2 the fungous elements have disappeared proximally where the drug has acted on the newly formed keratin. According to Davidson and Gregory,[8] the fluorescence with filtered ultraviolet light is due to a change in the hair after invasion by the fungus; it is limited to the portion invaded; and it is not present in the external mycelium surrounding the hair. It would seem reasonable to suppose that the course of therapy in tinea capitis could be reduced to two or three weeks if the fluorescent ends of infected hairs were clipped off as soon as a non-fluorescent band appeared at scalp level.

The results of therapy of tinea capitis due to zoophilic dermatophytes are not quite as impressive. In Case 1, a very early infection due to *M. canis*, a cure was attained with three weeks' treatment, and without the development of follicular pustules. In Case 2 the lesions were evident clinically at the time of first examination. This boy developed only a slight crusting at the follicular openings, and he was considered to be cured with three weeks' treatment. However, in Cases 3 and 4, typical follicular pustules developed in spite of

treatment with griseofulvin and the disease ran its usual protracted course. In both of these cases the fluorescence and fungi cleared from the infected hairs at the same rate as they did in all of the other cases. In Case 5, a boy with tinea corporis due to *T. mentagrophytes* also developed follicular pustules. The lesion was well established before therapy with griseofulvin was instituted. The treatment did not appear to affect the course of the disease.

According to Birt and Wilt,[9] the pus present in suppurative types of ringworm is a result of the allergic reaction of the tissues to the fungus, and bacterial antibiotic therapy does not affect it. Apparently this tissue response is also resistant to or unaffected by griseofulvin therapy.

This preliminary study would suggest that, if griseofulvin is as non-toxic as we have found it to be, it will become the treatment of choice for tinea capitis due to *M. audouini*, and for *M. canis* scalp infections if there is no follicular pustular reaction. Tinea capitis due to *M. canis*, with pustular response or kerion formation, will probably remain resistant to griseofulvin therapy, unless some other means can be found to overcome the tissue response, while the fungus is being eliminated from the hairs. This problem in therapy may also apply to tinea capitis due to *T. mentagrophytes* and *T. faviforme*.

SUMMARY

Griseofulvin, a new oral antibiotic for the treatment of superficial fungous infections, is described, and the difficulty of treating hairs invaded by fungi is discussed. Four cases of tinea capitis due to *M. canis*, two due to *M. audouini*, and one case of tinea corporis due to *T. mentagrophytes* were treated. Griseofulvin was non-toxic in the children treated. The infections due to *M. audouini* responded very quickly. Tinea capitis due to *M. canis* also responded favourably in the absence of follicular pustules. However, the drug does not appear to materially shorten the disease process when a follicular pustular reaction develops. In *M. canis* infections of the scalp, where a follicular pustular response is common, the infected hairs improved as expected, but the tissue response was not affected and the disease ran its usual protracted course.

REFERENCES

1. KLIGMAN, A. M.: *A.M.A. Arch. Dermat.*, 71: 313, 1955.
2. SABOURAUD, R. J. A.: Les teignes, Masson et Cie, Paris, 1910.
3. WILSON, J. W.: *In*: Fungus diseases—an International symposium, edited by T. H. Sternberg and V. D. Newcomer; Little, Brown & Company, Boston, 1955.
4. GENTLES, J. C.: *Nature*, 182: 476, 1958.
5. WILLIAMS, D. I., MARTEN, R. H. AND SARKANY, I.: *Lancet*, 2: 1212, 1958.
6. OXFORD, A. E., RAISTRICK, H. AND SIMONART, P.: *Biochem. J.*, 33: 240, 1939.
7. PAGET, G. E. AND WALPOLE, A. L.: *Nature*, 182: 1320, 1958.
8. DAVIDSON, A. M. AND GREGORY, P. H.: *Canad. J. Research*, 7: 378, 1932.
9. BIRT, A. R. AND WILT, J. C.: *A.M.A. Arch. Dermat.*, 69: 441, 1954.

RÉSUMÉ

La griséofulvine un nouvel antibiotique actif par voie orale est employée dans le traitement des infections superficielles causées par les champignons. La difficulté de la thérapie des invasions fongiques des cheveux est connue depuis longtemps et cependant l'auteur traita avec succès plusieurs cas de teigne dont quatre étaient dus au *M. canis*, deux au *M. audouini* et un au *T. mentagrophytes*. Les enfants ainsi traités n'accusèrent aucun symptôme d'intoxication par le médicament. La teigne du *M. audouini* réagit très rapidement et celle du *M. canis* aussi réagit favorablement en l'absence de pustules folliculaires. Lorsque ces pustules apparaissent le médicament ne semble pas diminuer sensiblement l'évolution de la maladie. Les lésions à pustules du cuir chevelu sont fréquentes dans les infections par *M. canis*. Les cheveux infectés s'améliorent dans ces cas mais la griséofulvine ne semble pas modifier la réaction tissulaire de sorte que la maladie poursuit comme d'habitude son cours prolongé.

---

## GRISEOFULVIN IN THE TREATMENT OF SUPERFICIAL FUNGOUS INFECTIONS

NORMAN M. WRONG, M.D.,*
MARK ROSSET, M.D., F.R.C.P.[C],†
ARTHUR L. HUDSON, M.D.‡ and
STEWART ROGERS, M.D.,¶ *Toronto*

IN DECEMBER 1958, the interest of all dermatologists was aroused by a short report by Williams *et al.*[1] in the *Lancet* on their results in the treatment of superficial fungous infections in man with an orally administered antibiotic, griseofulvin. Simultaneously, Blank[2] gave a verbal report on his results and this was amplified by a fuller report in March 1959.[3]

Since that time, groups of dermatologists in England, United States, Canada and throughout the world have been investigating this substance. If results obtained to date are substantiated by further investigation, the ideal fungicide for superficial fungous infections may have been found which will rank with penicillin in the treatment of bacterial infections. Like penicillin, griseofulvin may pave the way for a host of similar antibiotics, some of which may prove superior to the original.

Nearly a half century ago, Whitfield introduced an ointment which still bears his name for the treatment of superficial fungous infections. Since then, numberless ointments, lotions and paints have been introduced by private investigators, ethical pharmaceutical firms and non-ethical vendors of "cures". None of these substances which are used topically has produced any real or fundamental

*Division of Dermatology, Department of Medicine, Toronto General Hospital and Department of Medicine (Dermatology), University of Toronto.
†Division of Medicine (Dermatology), St. Joseph's Hospital, Toronto.
‡Division of Medicine (Dermatology), St. Michael's Hospital, Toronto.
¶Dermatology Clinic, Hospital for Sick Children.

improvement in therapy since Whitfield's ointment. The reason for this is probably that none of these substances penetrated to the area where the fungus was most active.

Wilson stated in 1955 that "a perfect fungicide . . . should be absolutely non-toxic to human beings . . . and active against all pathogenic fungi wherever they might be, in concentrations easily attained and maintained by oral or parenteral administration. . . . The *ideal* anti-fungal even for the superficial mycoses would seem to be one which could be safely administered internally in amounts sufficient to endow the cells eventually destined to produce keratin with power to resist fungi completely, this power persisting as they become keratinized and the drug thus exerting its effect from within outwards."

Griseofulvin was prepared in 1939 from *Penicillium griseofulvum dierckx* and also can be obtained from several strains of penicillia, but its value was not appreciated until Gentles[5] reported the cure of experimentally produced ringworm in guinea-pigs by the administration of griseofulvin orally. This was effective against *Microsporum canis* and *Trichophyton mentagrophytes* and later was found to be effective against *Trichophyton verrucosum* infection which had been experimentally produced in cattle.

Griseofulvin has been proved relatively non-toxic to the experimental animal even in huge doses. By April 1959, several thousand human subjects had been treated with this substance, with no serious toxic effects reported.[6] A lowered leukocyte count has resulted occasionally during therapy but this has promptly returned to normal even on continuation of the drug. Headache, nausea and transient erythemas have also been reported.

In December 1958, a supply of the antibiotic was made available* to the authors and also to several other university groups across Canada. Griseofulvin is prepared in a 250-mg. tablet administered orally. The ideal dosage schedule and the duration of treatment for cure are not yet known. Adults were given two grams daily in four doses, gradually reduced to one gram daily. Children were given approximately one-half this dose. Ringworm of the scalp (tinea capitis) has been treated for as short a period as three weeks with apparent cure, whereas *T. rubrum* infection of fingernails and toenails has been treated for four months with viable fungi still present.

The following are case reports of the first 10 patients treated in the Toronto area.

## CASE REPORTS

CASE 1.—This man, aged 49, was first seen in 1952 when a diagnosis of fungous infection of palms, soles, toenails and fingernails was made. It had been present nine years. Many topical remedies were tried with no appreciable effect except to lubricate the skin. In January 1959, he was recalled as a suitable prospect for griseofulvin.

At this time, both palms and palmar surfaces of fingers were red, thick and dry, and showed fine scaling. All fingernails were grossly abnormal except the left fifth. Nails were eroded, thickened, lustreless and opaque and there was much hyperkeratosis beneath the free margin. Soles were thickened, red, dry and scaly, and two toenails on the right foot and three on the left were grossly affected.

*Trichophyton rubrum* was cultured from palms, fingernails, soles and toenails. Leukocyte and differential counts were normal. Urinalysis normal. Liver function tests, van den Bergh and serum-glutamic oxaloacetic transaminase values were normal. All these tests gave normal results throughout therapy. Therapy commenced on January 15, 1959. Two tablets of griseofulvin (250 mg. each) were given four times daily for three weeks, then the dose was reduced to two tablets three times daily for four weeks, then to two tablets twice daily continued for duration of therapy. Total dosage at the end of April 1959 was 140 grams.

*After two weeks' therapy* there was less scaling, redness and dryness of fingers and the patient stated that there was more feeling in the fingers. Less scaling of soles was noted but there was no change in nails on feet and hands. Cultures of *T. rubrum* were still positive from palms, soles and nails.

*After three weeks' therapy,* finger and palms felt normal to the patient for the first time in years. There was almost no redness and scaling of palms and soles. The fingernails showed slight improvement.

*After six weeks' therapy,* palms and soles appeared almost normal. The lunulæ of some fingernails showed normally. *T. rubrum* was cultured from both fingernails and toenails.

*After nine weeks' therapy,* all fingernails showed two-thirds of the proximal portion normal. There was still some crumbling at the free margin. Toenails showed much less improvement. Cultures from palms, soles and nails were negative.

*After twelve weeks' therapy,* fingernails were all practically normal. The palmar surfaces of the fingers were normal except for slight scaling in a few small areas. The skin of the soles appeared normal, as did the plantar surface of toes. Toenails were normal for the proximal one-third but the distal two-thirds was still opaque, discoloured and eroded.

This patient had had his disease for nine years before therapy was instituted, and topical remedies had been tried without avail. At the end of three weeks' treatment there were subjective and objective improvements in palmar and plantar skin, there being little or no scaling or redness, and some sweating had returned. At the end of 12 weeks fingernails were practically normal and toenails were one-third improved. There were no toxic manifestations from the drug.

CASE 2.—A man aged 43 had dryness of the skin of the right thumb and both soles, gradually increasing. The right thumbnail had become eroded, almost to the lunula. Toenails on both feet were yellowish, opaque and crumbling at the free edge. Many local remedies had been tried without any real effect. The condition had been present for 2½ years. At examination

*By Mr. L. A. Gullick of Glaxo-Allenburys (Canada) Ltd.

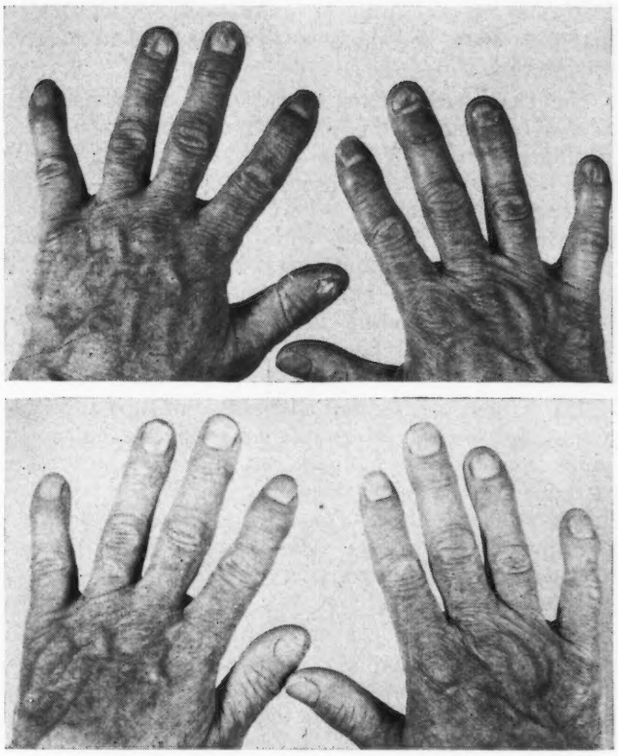


Fig. 1a.—Case 3. Fingernails before therapy.
Fig. 1b.—Case 3. Fingernails after four months' therapy.

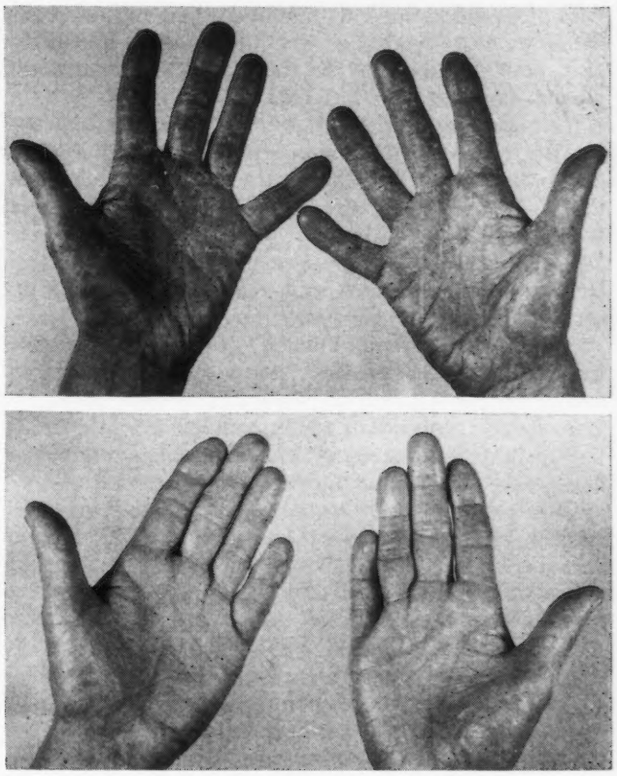


Fig. 2a.—Case 3. Palms before therapy.
Fig. 2b.—Case 3. Palms after four months' therapy.

in January 1959, the right thumbnail was eroded and crumbling, the distal portion opaque. The skin of the right thumb was dry, red and scaly. Both soles were dry, red and scaly, also the sides of the heels. Great toenails and two other toenails on each foot were yellowish and opaque, with hyperkeratosis beneath the nails.

*Trichophyton rubrum* was cultured from the right thumbnail, palmar skin of thumb, both soles and several toenails. Leukocyte count, urine and liver function (van den Bergh and serum glutamic oxalo-acetic transaminase tests) were normal and remained normal for the duration of therapy.

Griseofulvin, two tablets (250 mg. each) four times daily, was given for two weeks, then three times daily after meals for four weeks, then twice daily continued. Total dosage to April 1959 (3½ months of therapy) 126 grams.

*At the end of two weeks' therapy,* the skin of the thumb and soles was less red and scaly and was subjectively improved. Mycological cultures were positive for *T. rubrum*. Headache, nausea and feeling of depression were pronounced. The evening dose of the drug was stopped and these symptoms promptly disappeared.

*After four weeks' therapy,* the skin of the thumb and of soles appeared almost normal. The thumbnail was definitely improved. No change was noted in the toenails. Cultures from the plantar skin were negative, from the toenails positive.

*After eight weeks' therapy,* no redness and scaling of the skin of the thumb or the soles were noted. The thumbnail appeared normal for its proximal one-half. Some toenails were clear at the lunula. Cultures were negative for *T. rubrum*.

*After ten weeks' therapy,* the thumbnail was normal for its proximal two-thirds. The skin looked and felt normal. Toenails showed definite clearing in the proximal one-quarter. Cultures from toenails were positive for *T. rubrum*.

*After 14 weeks' therapy,* the thumbnail was practically normal. The skin of the thumb, soles and sides of the heel looked and felt normal. Affected toenails were normal for the proximal one-third. The distal two-thirds were still yellowish and opaque and crumbled easily.

After two years of disease with no response to topical remedies, the patient began to show improvement within three weeks and this was maintained during 14 weeks of therapy. Toxic symptoms consisted of headache, nausea and feeling of depression which cleared immediately when the night dose of drug was discontinued. Improvement continued on one gram of griseofulvin daily.

CASE 3.—This 56-year-old physician first developed a fungous infection of his feet 30 years ago. This spread to involve his hands and fingernails within a few months. During the past 25 years, numerous fungicidal and fungistatic remedies had been used without effect. Recently the disease had become stationary.

On examination before present therapy, all nails of both feet and hands were found involved, some of them being almost totally destroyed, others only partially. The palms and soles were thickened, red, scaly and at times fissured. There was considerable itching of palms and soles. The remainder of the skin appeared normal.

Cultures from fingernails and toenails, palms and soles were positive for *Trichophyton rubrum*.

Therapy was commenced on January 18, 1959, with two tablets of griseofulvin (250 mg. each) four times daily. This dose was reduced after four weeks to six tablets daily. Later a reduction to four tablets daily

was attempted, but this resulted in increased scaling of the palms. The dosage was increased to eight tablets and later reduced to six tablets daily, and steady clinical improvement has resulted.

Total dosage to May 14, 1959, 152 grams (approx.).

After ten days, there was less redness of the fingers and palms. After four weeks there was less accumulation of debris beneath the fingernails and toenails, and the soles were almost free of scaling and redness. The palms were almost normal and the patient said he had more sensation in his fingers and there was some sweating for the first time in years.

Three and a half months of therapy produced fingernails which were 75% normal and toenails about 40% normal. Attempted reduction of the dosage of griseofulvin resulted in more scaling.

Four months of therapy has produced normal fingernails except for slight hyperkeratosis beneath them.

Cultures for *T. rubrum* were negative after 3½ months. Leukocyte count, urine and liver function remained normal throughout therapy.

No side effects were noted during therapy, except for slight redness of the nose with a few papules (mild rosacea). This did not increase during therapy.

In summary, this 56-year-old physician had had *T. rubrum* infection of palms, soles, fingernails and toenails for 25 years. Four months of treatment produced remarkable improvement in his fingernails and also in palms and soles. Toenails were about 50% improved.

CASE 4.—This man, aged 30, had had an eruption affecting the nails, left palm and soles for over three years. It was pruritic and associated with marked dryness and scaling. He had used multiple fungistatic preparations and superficial x-ray therapy with only temporary improvement.

Physical examination showed a pale erythema with dryness and slight scaling of the left palm and both soles. Most of the toenails and the left third fingernail and left thumbnail showed irregular thickening and scaling under the free edges. Microscopic examination showed the presence of mycelium in scrapings from the left palm, but no fungus was grown on culture. Cultures from the soles grew *T. rubrum*.

He was started on griseofulvin, 1.5 g. daily, on March 5, 1959. Within three weeks there was marked improvement, with disappearance of erythema and scaling; the patient volunteered the information that the left palm felt normal and, for the first time in many years, was perspiring as well as the right one. After one month of treatment, the dosage was reduced to 1 g. daily and the clinical improvement maintained. There was slow and gradual clearing of the nails, and all the microscopic examinations and cultures were reported as negative up to two months after the treatment was started. There were no side effects and results of routine blood examinations and urinalyses were within normal limits on several occasions.

CASE 5.—A man, aged 46, had complained for about two years of an eruption affecting some of the fingernails, which were described as "brown, loose and thickened"; no subjective symptoms were associated with this condition. Another complaint was of the presence of redness and dryness of both palms (for 2-3 years), complicated in the last few months by the appearance of scaling. The patient mentioned that there was practically no perspiration of his hands and that they were becoming so dry that he had to give up bowling.

On examination, there was pale erythema with marked scaling of the palms and palmar aspect of all fingers. The right thumbnail was almost completely destroyed, with a few irregular ridges left and with dryness and scaling of the nail bed. Most of the other fingernails were affected, with irregular furrows and distal scaling. Scrapings showed the presence of mycelium, but the cultures failed to identify the fungus. A complicating factor was the presence of lesions of psoriasis (25 years' duration) on the trunk and scalp.

The patient was treated with different topical preparations and superficial x-ray therapy to the nails. His hands remained unchanged, but the nails showed a marked improvement. However, after one year of this treatment, cultures from the palms were reported as growing *T. rubrum*. Microscopic examination of scrapings from the fingernails revealed the presence of mycelium, but again there was no growth on culture.

He was started on griseofulvin 1.5 g. daily; after two weeks of treatment, there was little clinical change, but the patient noticed less dryness and stated that his hands "felt like they were going to perspire". Within one month, there was no dryness and very little scaling present on the palms; some of the fingernails were showing a few mm. of normal growth. There was no mycelium on microscopic examination of the scrapings from the palms, but it was still present in the scrapings from the nails.

There were no side effects, and results of routine blood examinations and urinalyses were within normal limits.

CASE 6.—Since the age of 15, this woman, now aged 29, has had recurrent episodes of "athlete's foot". These attacks consisted largely of fissure formation between toes and peeling of the soles, without any vesicles. She was treated with different ointments and foot baths; she was never entirely free of scaling, although symptoms of burning and itching would appear only in the summer months. At the age of 19, she first noticed involvement of the toenails, and several years later the right middle finger and fingernail became affected with scaling and erythema. In 1957-58, she had most of the available fungicidal preparations and superficial x-ray therapy, with marked improvement of the right 4th fingernail (which became involved in 1958).

Examination before treatment with griseofulvin was started showed erythema and scaling of both soles extending to the sides, heels and interspaces between the toes. All toenails were involved to varying degrees, and the right 3rd fingernail was split longitudinally with subungual lifting of the nail and an opaque white discoloration. Cultures from all the affected areas grew *T. rubrum*.

She was started on griseofulvin on March 4, 1959, and received 2 g. for one week, the dosage being reduced gradually to 1 g. daily (one tablet four times a day). Within two weeks, the scaling of the soles had almost completely gone. Since then she has had recurrent episodes of increased scaling, but in general is comfortable with no itching or burning despite a nine-day visit to Bermuda at the onset of therapy.

After one month of treatment, it was evident that the fingernail was regrowing and a small ridge of new growth was visible on the toenails. At the end of two months of therapy, one-half of the fingernail was new and normal in appearance; the toenails were much slower in growth. Four weeks after treatment started, the cultures were still positive; after eight weeks there was no mycelium on microscopic examination of the finger and toenails, but it was still present in the scrapings from the feet.

There were no side effects; blood and urine were normal.

CASE 7.—This man, aged 65, was first seen in May 1956, with the history of an extensive eruption present for four months. At that time, he had a diffuse erythematous rash involving the shoulders, upper back, groins, legs and feet. Some of the toenails were affected, with furrowing and thickening. Scrapings from all the affected areas showed the presence of *T. rubrum*. He improved much at first with topical therapy; he was seen again with a recurrence (and involvement of the face) in October 1956. From then until December 1958, he was treated with multiple preparations with marked improvement at times, but all cultures remained positive. There was no result from a series of gamma globulin injections.

On December 23, 1958, the trunk and upper limbs showed multiple small patches of pale erythema with slight scaling. Similar, large, more diffuse lesions could be seen on the scalp, face and lower limbs. There was scaling of most of the toenails; the left thumbnail and the right fifth fingernail showed distal and lateral deformities with scaling and brittleness. Cultures from all affected areas grew *T. rubrum*, except for the fingernails, where *Candida albicans* was found (although clinically the lesions looked like *T. rubrum* infection).

He was started on griseofulvin, 2 g. daily; there was marked clinical improvement within one week, after which the dose was reduced to 1.5 g. Seen again one week later, he was slightly worse, so the dose was increased again to 2 g. On January 27, 1959, there was another slight clinical flareup and the patient was advised to take 2.5 g. daily. Since then there has been very little scaling, although a few small patches of erythema could still be seen, mostly on the face and upper trunk. After three weeks of treatment, all cultures were negative except for the right foot (*T. rubrum*) and the left arm (*Candida albicans*).

After 7-10 weeks of treatment, all cultures were negative for *T. rubrum*, but many areas grew *Candida albicans*. The dose of griseofulvin was then gradually reduced to 1 g. daily and the patient was given nystatin (Mycostatin) ointment for applications to the regions affected by *Candida albicans*. Within 4-6 weeks, gradually and while the patient was still under treatment, several areas showed a slight clinical flare-up (increased scaling) and presence of *T. rubrum*. At the same time, *Candida albicans* seemed to have disappeared (or failed to grow) from the *T.-rubrum* infected regions. The fingernails kept improving, with only the distal few mm. showing involvement. This situation remained unchanged over a period of two months of treatment with 1 g. of griseofulvin. Three weeks before this report was written (mid-May), the daily dosage was increased to 2 g., again with marked clinical improvement (less scaling and less erythema), but microscopic examinations were still showing presence of mycelium.

Blood, liver function and urine, studied on several occasions, were reported as within normal limits. There were no side effects.

CASE 8.—This boy, aged three years, had two areas, each 2 cm. in diameter, on the scalp posteriorly showing subacute inflammation with broken hairs. There was moderate itching. The rest of the skin was clear. Wood's light examination was positive for fluorescent hairs.

Culture of the hair grew *Microsporum audouini*. It was subsequently found that a pet monkey had ringworm, which may have been the source of infection. Leukocyte count and urine were normal.

Griseofulvin, one tablet (250 mg.) three times a day, was given for three weeks (total dose 16 grams). Itching and redness disappeared in ten days. Wood's light examination was negative on the 20th day and remained negative.

In summary, this *M. audouini* infection of the scalp in a three-year-old with some inflammatory reaction cleared and remained clear with three weeks' therapy.

CASE 9.—This 38-year-old farmer's wife developed widespread ringworm infection on March 23, 1959. She had been in close contact with her two boys, who were under treatment for kerion of the scalp, and their cattle were under treatment for ringworm. There were extensive circinate and follicular lesions on the face, left shoulder, upper arm and left thigh. Direct microscopic examination and preliminary laboratory report showed the presence of mycelium. Cultures failed to grow.

Local treatment was carried out for one week with 10% sulphur ointment and one week with Whitfield's ointment. During this period the condition extended to involve new areas, including the face. Griseofulvin, 2 g. daily, was started on April 3. The patient complained of severe headache, and dosage was reduced to 1.5 g. daily after one week. Microscopic examination and culture were negative seven days after starting griseofulvin. Treatment was continued for a further 14 days, at which time she was completely clear.

Leukocyte count, urine and liver function were normal before therapy and remained normal throughout.

In summary, this patient with extensive ringworm of the glabrous skin improved rapidly on griseofulvin after failing to be influenced by two weeks of local therapy. There were no changes in the laboratory findings. The patient suffered with headache while taking griseofulvin; her headache was intolerable on 2 g. a day but tolerable on 1.5 g. daily. Total dosage 35 g.

CASE 10.—This 9-year-old boy was examined on February 11, 1959, at the Hospital for Sick Children. He was suffering from tinea capitis with involvement of the left parietal and occipital areas. These areas showed broken hairs and superficial scaling of the scalp but there was very little inflammatory reaction. Wood's light examination was positive. Direct microscopic examination showed the presence of mosaic spores. Culture grew *M. canis*.

Treatment was started on February 28, 1959, with 1 g. of griseofulvin daily. Cultures were repeated weekly and the first negative culture was obtained 60 days later.

Leukocyte count, urinalysis and liver function tests were carried out on this patient before, during and after treatment, and no significant change was detected in the results.

In summary, this patient's non-inflammatory *M. canis* infection cleared after eight weeks' treatment with griseofulvin. There were no unpleasant symptoms and no significant changes in the laboratory findings. Total dosage 60 g.

## DISCUSSION

Of the 10 cases reported, seven were of *Trichophyton rubrum* infections, in all of which the fungus was identified by culture. In six of these cases the palms, soles and nails were involved and in the other case there was a widespread infection of trunk and extremities. One patient had an unidentified fungous infection of her shoulder and thigh, probably acquired from cattle. One child had a *Microsporum audouini* infection of the scalp, possibly acquired from a pet monkey, and this responded quickly to therapy. The other child had a non-inflammatory *Microsporum canis* infection of the scalp which responded very slowly to therapy but finally cleared.

Toxic symptoms consisted of headache and a mild erythema of the nose. The headache in the male patient disappeared as soon as the evening dose of the drug was discontinued, but it continued in the female patient with the elimination of the evening dose although it was less severe. There were no other toxic symptoms, and no reduction in leukocyte count, or changes in results of liver function tests or in urinalyses were noted.

Cultures of *T. rubrum* remained positive for a long time and there were positive cultures from the toenails in one case after 14 weeks of therapy even with considerable clinical improvement. Blank and Roth[3] noted that griseofulvin is not fungicidal *in vitro* and it apparently exerts its effect as a fungistatic agent *in vivo*. As the fingernails and toenails may act as a source of continuing infection, it may be wise in the future to advise patients to have all the infected nails avulsed before commencing therapy. This might reduce the time necessary for cure, but is a heroic measure when many nails are involved.

The improvement in the palms of the hands is an early and dramatic change. With less redness, scaling and thickening, patients note an increase of normal sensation in the finger-ends, and increased sweating of the palms and the fingers, which in one patient had been absent for over 20 years.

It is hoped that this treatment will prove effective in the control and cure of ringworm of the scalp (tinea capitis). If so, epidemics may be a thing of the past and the need for x-ray depilation of scalp hair to cure Microsporum infections may be no longer necessary.

Many reports will no doubt be forthcoming on this new and remarkable antibiotic. It is to be hoped that it will not develop severe side effects with use, and also that there will be no drug-resistance of fungi comparable to that developed by the staphylococcus against antibiotics.

Work to date has shown[3] that it is effective against the Trichophyton family, as well as Microsporum and Epidermophyton, but has no effect on *Candida albicans* (Monilia). It is essential that the fungus should be demonstrated microscopically and culturally before treatment is instituted. This antibiotic is not the cure-all for "athlete's foot" when this term is used glibly for all eruptions of the feet without proper diagnosis and laboratory confirmation.

This antibiotic, like most new ones on the market, will probably be expensive when first released. It should be properly used and not abused and it is hoped that it will be available to patients on physicians' prescription only. The proper dosage and duration of therapy to produce cure will only be determined by continued investigation.

## SUMMARY

Ten patients were treated with griseofulvin orally. These included seven patients with *Trichophyton rubrum* infection, in all of which there was dramatic improvement. In none of them could it be stated that a permanent cure was obtained. One patient still showed viable fungi on culture from the skin after five months' therapy and one in cultures from toenails after 4½ months' therapy. These cases will be followed up and reported later if found to be resistant to treatment.

Two patients with ringworm of the scalp (tinea capitis) were apparently cured, but one was very slow in responding.

No serious side effects were noted except for severe headache in two patients and a mild erythema of the nose in one patient. Another patient developed moniliasis in areas formerly infected with *T. rubrum* but this improved with nystatin ointment.

This new antibiotic has great promise in the treatment of superficial fungous infections, but it is too soon to determine whether it will cure or merely control.

Case 6 was provided by Dr. R. K. Schacter and Case 8 by Dr. Raymond C. Smith. The mycological studies in the main were done by Mr. John Fischer, mycologist, Central Laboratory, Provincial Department of Health of Ontario.

## REFERENCES

1. WILLIAMS, D. I., MARTEN, R. H. AND SARKANY, I.: *Lancet*, 2: 1212, 1958.
2. BLANK, H.: Griseofulvin in superficial fungus infections. Paper read at 17th Annual Meeting of the American Academy of Dermatology and Syphilology, Chicago, December 6-11, 1958.
3. BLANK, H. AND ROTH, F. J., JR.: *A.M.A. Arch. Dermat.*, 79: 259, 1959.
4. WILSON, J. W.: Possible approaches to the therapy of fungus diseases. *In*: Fungus diseases—an international symposium, edited by T. H. Sternberg and V. D. Newcomer, Little, Brown and Company, Boston, 1955, p. 25.
5. GENTLES, J. C.: *Nature*, 182: 476, 1958.
6. WILLIAMS, I.: Personal communication.
WALKER, H. M.: Personal communication.

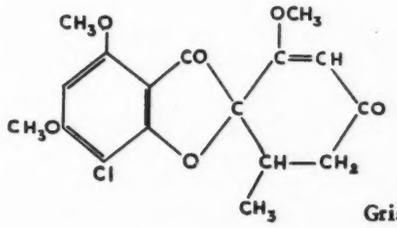
RÉSUMÉ

Sept malades porteurs d'infection au *Trichophyton rubrum* ont tous montré une amélioration impressionnante après avoir reçu de la griséofulvine oralement. Chez aucun d'entre eux cependant peut-on prétendre qu'une guérison définitive ait été obtenue. Après cinq mois de thérapie on pouvait encore prélever des champignons viables de la peau d'un d'entre eux et des ongles d'orteil d'un autre après quatre mois et demi de médication. Ces cas seront gardés en observation et formeront l'objet d'un autre rapport si la résistance au traitement persiste. Deux autres malades atteints de la teigne (*Tinea capitis*) ont semblé guéris mais chez l'un d'eux la guérison a été très lente. Les incidents du traitement ont inclus quelques céphalées assez intenses chez deux malades et un léger érythème du nez chez un autre. Dans un cas l'infection au *T. rubrum* a été remplacée par une moniliase localisée aux endroits déjà infectés; cet état s'est amélioré par l'emploi d'onguent à base de nystatin. La griséofulvine offre de grandes promesses dans le traitement des infections fongiques superficielles mais il est encore trop tôt pour savoir si elle guérira ces infections ou ne servira seulement qu'à les tenir en respect.

# GRISEOFULVIN, A NEW ORAL ANTIBIOTIC FOR THE TREATMENT OF FUNGOUS INFECTIONS OF THE SKIN*

ANNA FLINT, M.D., R. ROY FORSEY, M.D., F.R.C.P.[C] and BARNEY USHER, M.D., C.M.,
*Montreal*

A NEW oral antifungal agent has recently been made available for the treatment of dermatomycoses—griseofulvin, a stable white crystalline odourless solid with low solubility in water, with the formula:




Griseofulvin

Griseofulvin was first isolated in 1939, by Oxford, Raistrick and Simonart[7] from culture of *Penicillium griseofulvum dierckx*. In 1946, Brian *et al.* obtained an antibiotic from cultures of *Penicillium janczewskii*, which produced changes in the morphology of several species of fungi; they called this antibiotic "curling factor", and it was later shown to be identical with griseofulvin.[3] The antifungal properties of griseofulvin found their first application in agriculture, when the substance was shown to protect crops of lettuce and tomatoes from invading fungi.[10]

In 1955, workers at Glaxo Laboratories found the substance to be very active *in vitro* against pathogenic skin fungi. Topical applications of griseofulvin in ointment form were unrewarding, however, and were no improvement over the use of the older fungistatic agents such as Whitfield's ointment.

In 1958, Gentles[4] published a report on the oral administration of griseofulvin in experimental fungus infections in guinea-pigs. Microsporon and Trichophyton infections were successfully treated with this drug. Several months later, Riehl[11] in Austria, Williams[12] in England and Blank[1] in the United States first used the drug in human subjects and obtained near-miraculous results.

At the Montreal General Hospital we have treated a number of cases of ringworm of the scalp, nails and skin, with results comparable to those obtained by the above authors.

## CLINICAL OBSERVATIONS

1. *Ringworm of the scalp* in three children of the same family, aged 5, 7 and 9 years, was treated with griseofulvin 250 mg. 4 times a day. The children's infected hair was positive to Wood's light. The culture yielded *Microsporon canis*. Three weeks after onset of therapy the treatment was interrupted when the patients failed to report for their supply of pills, because they had upper respiratory infections. When they reported two weeks later, the Wood's light examination showed the infected hair to be normal at the base and fluorescent at the tips. After two more weeks of treatment all three children were free of infection. The cultures became negative. The patients had not required epilation and the scalp remained clear one month after therapy was discontinued.

2. *Ringworm of the nails* was treated in four patients. All showed dystrophy of several fingernails and toenails of many years' duration, resistant to previous forms of therapy. The fungus cultures were positive for *Trichophyton rubrum* in three cases and for *Trichophyton mentagrophytes* in one case. Griseofulvin was given in a dose of 250 mg. 4 times a day.

In all cases the nails became normal pinkish in colour and smooth near the root after about four to five weeks of treatment, and gradually grew out normally as treatment was continued, being about 50% improved in nine to ten weeks of therapy. The cultures were still positive when scrapings were taken from the dystrophic fingertips. In one case followed up for four months, the nails were normal even though treatment had been interrupted a month previously. Cultures in this case became negative.

3. *Ringworm of the feet* was treated in two patients with griseofulvin 250 mg. 4 times a day.

*Read before the Annual Meeting of the Canadian Dermatological Association, Montreal, June 5, 1959.

From the Department of Dermatology, Montreal General Hospital, Montreal, Quebec.

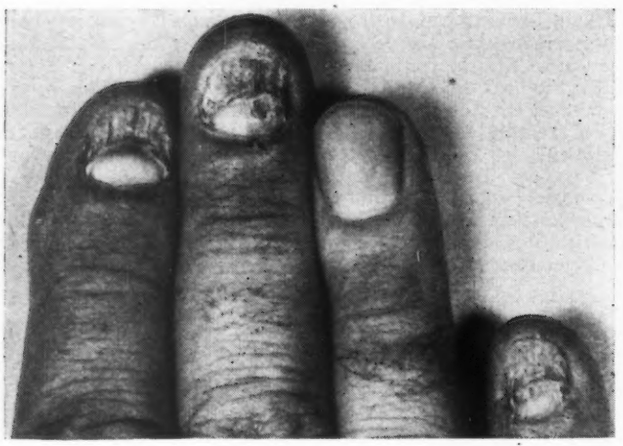


Fig. 1a.—Fingernails before treatment.

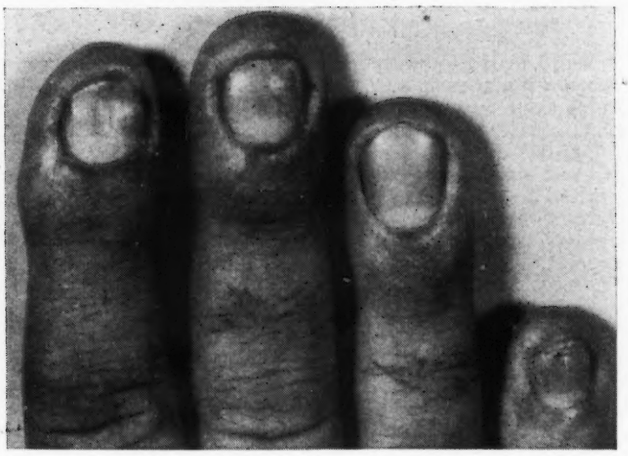


Fig. 1b.—Fingernails three months after oral treatment with griseofulvin.

The first patient was a 44-year-old man with an acute vesicular eruption of the soles in discoid patches, of one week's duration. The fungus smear was positive. The culture yielded *Trichophyton mentagrophytes.* The patient was first treated with potassium permanganate soaks and wet dressings. Two weeks later, the lesions were spreading with vesiculation at the borders. He was then started on griseofulvin. One week later the lesions were dry and squamous. Two weeks later further improvement was noted as the areas became less scaly. Three weeks later many areas were free of involvement. The patient is still under treatment.

The second patient was a 58-year-old woman with an acute vesicular dermatitis of the distal parts of the feet of six months' duration, and widespread "id" reaction over the thighs and arms. *Trichophyton rubrum* was isolated from the feet. The lesions were secondarily infected with *Staph. pyogenes, Strep. zymogenes* and *E. coli.* Griseofulvin was given in a dose of 500 mg. 4 times a day, later reduced to 250 mg. 4 times a day. Because of the secondary infection she also received a course of tetracycline. She responded poorly to this treatment, and showed progress only after about five weeks on griseofulvin. Improvement was rapid, however, after the patient was also given triamcinolone. Two months after the beginning of treatment, she was free of eruption, and fungus cultures became negative.

None of our patients reported any side effects from the drug.

## DISCUSSION

### *Mode of Action of Griseofulvin*

*In vitro* studies have shown that griseofulvin disturbs the metabolism of fungi by direct contact.[3, 9] The fungal hyphæ become distorted in the form of spiral curling to severe stunting. Weak spots appear on the cell wall and frequently rupture. There is no diffusion through the hyphæ, as shown by the fact that hyphæ contiguous with the inhibited zones but not in direct contact with the drug will develop normally. This explains why the treatment has to be prolonged until the infected keratin material has been shed.

When given orally the drug is absorbed through the gut, as proven by assays done with $Cl^{36}$-labelled griseofulvin. It is not yet clear whether the drug is absorbed in its original form; neither is it clear whether it is excreted in the urine. It has been demonstrated however in keratin material of treated animals.[5] Griseofulvin is active only against the dermatophytic group of fungi, including Microsporon, Trichophyton and Epidermophyton species. It is ineffective against *Tinea versicolor,* Monilia and the deep fungous infections. It is not an antibacterial antibiotic and its prolonged administration will not disturb the normal intestinal flora.

### *Toxicity*

All investigators[1, 4, 6, 8, 11] are unanimous in stating that the drug is of very low toxicity. The median lethal dose in rats is 400 mg./kg. intravenously, and doses of 2000 mg./kg. given intraperitoneally for several days are well tolerated.[8]

However, when given in sublethal doses in rats (100 to 200 mg./kg. intravenously) griseofulvin will arrest mitoses in rapidly growing tissues. The effect is marked in the seminal epithelium, the bone marrow and the intestine and also in transplanted carcinoma or lymphosarcoma.[8]

When given orally, rats will tolerate single doses of 10 g./kg. without adverse effects. Effective therapeutic doses in humans are of the order of 15 to 20 mg./kg., so that we should hardly expect any toxic effects. Riehl[11] in Vienna found no abnormalities in the blood picture, liver function, blood urea, blood sugar, sedimentation rate and urine of 15 patients studied during therapy. Blank found no depression in sperm counts, as well as no significant change in blood counts of patients under treatment.[2] The only side effects of griseofulvin appear to be of a minor nature: gastro-intestinal complaints, sometimes headaches, which seem to subside even though therapy is continued. The rare case of urticaria has been reported.

### *Results*

The effective therapeutic dose for the average adult is about one gram a day. Some workers have

been successful with even lower doses. The average length of treatment for infections of the nails would appear to be of the order of four to six months. Scalp infections require from three to four weeks, and the patient's hair should be cut in order to eliminate the infected tips. Ringworm of the glabrous skin should also require from three to four weeks of treatment, perhaps longer when the thick keratin layer of the feet is involved. In cases where eczematization has occurred or when secondary bacterial infection is present, the treatment should be supplemented with adequate topical or internal therapy.

### SUMMARY AND CONCLUSIONS

A clinical trial with the oral antibiotic griseofulvin in the treatment of ringworm of the nails, scalp and skin is reported.

This drug has been found very effective in Trichophyton and Microsporon infections.

It appears to be particularly valuable in clearing up stubborn and resistant cases of tinea unguum, heretofore almost impossible to cure, especially those infected with *Trichophyton rubrum*. While the drug is effective in all superficial cutaneous mycoses, it is in the field of nail infections that the results are most striking.

From the public health point of view, the advent of an effective oral antifungal agent may well help to eradicate epidemics of ringworm in human subjects, as well as the reservoir in domestic animals and cattle.

Because of its low toxicity, the temptation will be great to use it in an indiscriminate fashion, or as a therapeutic test. We feel that such a useful drug would be devaluated if it were to be used blindly. We also wonder whether—as has happened with other antibiotics—one may not expect the development of resistant strains of fungi. The use of griseofulvin should be limited to properly diagnosed cases, confirmed by culture.

We wish to thank the Glaxo Company for kindly supplying GRISOVIN (brand of griseofulvin) (distributed by UNIK in Quebec) for this study.

### REFERENCES

1. BLANK, H. AND ROTH, F. J., JR.: *A.M.A. Arch. Dermat.*, 79: 259, 1959.
2. BLANK, H.: Personal communication, May 1959.
3. BRIAN, P. W., CURTIS, P. J. AND HEMMING, H. G.: *Trans. Brit. Mycol. Soc.*, 29: 173, 1946.
4. GENTLES, J. C.: *Nature*, 182: 476, 1958.
5. GENTLES, J. C., BARNES, M. J. AND FANTES, K. H.: *Ibid.*, 183: 256, 1959.
6. LAUDER, I. M. AND O'SULLIVAN, J. G.: *Vet. Rec.*, 70: 949, 1958.
7. OXFORD, A. E., RAISTRICK, H. AND SIMONART, P.: *Biochem. J.*, 33: 240, 1939.
8. PAGET, G. E. AND WALPOLE, A. L.: *Nature*, 182: 1320, 1958.
9. Special Article: *Pharm. J.*, 182: 279, 1959.
10. Report on Griseofulvin: A review of properties and formulation for agricultural purposes, Glaxo Laboratories Ltd., December 1955.
11. RIEHL, G.: Griseofulvin, an orally active actinomycotic. *In*: Communication to meeting of Oesterreichische Dermatologische Gesellschaft, November 27, 1958.
12. WILLIAMS, D. I., MARTEN, R. H. AND SARKANY, I.: *Lancet*, 2: 1212, 1958.

### RÉSUMÉ

La griséofulvine s'est montrée très efficace dans le traitement de l'infection des ongles, du cuir chevelu et de la peau par le Trichophyton et le Microsporon. Jusqu'à présent les infections unguéales à *T. rubrum* étaient reconnues comme rebelles à presque toutes les formes de traitement; ce nouvel antibiotique oral semble en avoir raison. La griséofulvine devrait contribuer à éliminer la teigne chez l'homme et chez l'animal. Sa toxicité très basse menace de provoquer des abus qui pourraient produire l'émergence de souches résistantes. Il importe donc que son emploi soit réservé aux cas correctement diagnostiqués et confirmés par le laboratoire.

---

## THE PRESENT STATUS OF CONTROL OF MANUFACTURED ANTIBIOTIC SENSITIVITY DISCS*

ARNOLD BRANCH, M.D.,
D. H. STARKEY, M.D. and
EDNA E. POWER, B.A.,
*Saint John, N.B.* and *Montreal*

THE TESTING of sensitivity of pathogenic bacteria to antibiotics has become a necessary procedure in hospital laboratories. The laboratory tests are for the purpose of aiding the clinician in his choice of therapy for infections of all types, since concentrations used *in vitro* are set to correspond with blood levels obtained *in vivo*.

The greater demand for antibiotic sensitivity tests is due to the increasing number of antibiotics becoming available to physicians for use in treatment of infections. It is also due to the development of resistant strains, as well as the great variation in the sensitivity of individual strains within certain bacterial species.

Studies by many medical research workers in the antibiotic field have shown that laboratory results and clinical response to therapy can be made to show good correlation. However, there are instances when lack of correlation is reported, and one cause of this may be a faulty *in vitro* test.[1]

There are two basic methods in common use for determining bacterial sensitivities to antibiotics: (1) the serial dilution method, in liquid or solid media; (2) the agar diffusion method. The depot may be a cup, well, ditch, cylinder or disc. The most commonly employed method at the present time is the use of impregnated tablets or paper discs, either commercially prepared or home-made. Some of these latter tests are done with single discs, others with sets of two concentrations. Multi-tipped discs are also available, impregnated commercially or home-made.

*From the laboratories of the Department of Veterans Affairs Hospitals, Saint John and Montreal.

The importance of controlling all variable factors in performing *in vitro* antibiotic sensitivity tests cannot be overemphasized, since variations can affect the results of the tests. Some of these are: the size of inoculum, the pH, composition, depth and moisture of the culture medium, the length of incubation and the rate of release of antibiotic into the agar and the rate of diffusion in agar.

If all these conditions are standardized for the various methods, comparable results may be obtained.[2] Two very important factors, which tend to be overlooked or taken for granted in the agar diffusion method employing discs or tablets, are: (1) The choice of optimal amounts of antibiotic for them. These concentrations must be adequate for outlining the varying degrees of sensitivity (sensitive, moderately resistant and resistant).[3] (2) Correspondence between assayed content and labelled potency.

One further cause of error is in the interpretation of the *in vitro* results. "*Sensitive*" should mean that the bacteria are easily affected by the antibiotic and treatable with ordinary dosages. "*Moderately resistant*" should indicate that the drug is less effective against the bacteria but high dosage may clear the infection. "*Resistant*" should indicate that, even with a high dosage, the drug would be ineffective in therapy. These categories may be defined in reading the test by measuring the size of the zone of inhibition around a single disc. Another method of interpretation, using two discs of different concentrations, is to consider any zone as significant and to employ its presence irrespective of size, around the low or high concentration, to indicate the degree of sensitivity.

A survey of methods used in Canada for antibiotic sensitivity testing was undertaken by this laboratory. It confirmed the fact that manufactured discs or tablets are used in practically all laboratories.[4] The disc method also is used to a great extent throughout the world, since it is less time-consuming than the other methods. Discs are manufactured in England, France, Sweden, Switzerland, Denmark, Poland, Germany, Czechoslovakia, Japan, Hungary, Italy, Uruguay and the United States, as well as some other countries, and are distributed to other parts of the world. It will thus be seen that careful control of their potency is of considerable importance, as they are used in the laboratory without preliminary assay and their labelled potency is confidently accepted as the actual content.

Observations of discrepant results obtained with discs of all manufacturers selling in Canada (United States manufacture) were made in this laboratory several years ago.[5-7] The finding that the assayed potency did not always conform to the labelled potency was confirmed by the Laboratory of Hygiene in Ottawa.[8] Wide variations were observed with all antibiotic discs and tablets of all manufacturers. Extensive investigations were carried out in both laboratories, and as a result, in 1957, antibiotic sensitivity discs sold in Canada were placed under the Canadian Food and Drugs Act and had to meet certain minimum requirements before being sold in this country. In 1958, the American Food and Drug Administration, after receiving complaints of discrepant results with discs used in the U.S.A., made a study of sensitivity discs and tablets of American manufacturers and found also that a great many of them were either over or under labelled potency.[9] The United States Food and Drug Administration has recently taken steps to eliminate this hazard, and to ensure that manufactured discs sold in that country come up to carefully defined performance standards.

As the result of work done in both countries, antibiotic sensitivity discs sold in Canada and the United States must meet standards of potency, quality, purity and performance. Also, specified requirements for expiry date, packaging and labelling and tests and methods of assay are laid down. A recent publication from Great Britain indicates that penicillin tablets manufactured there and widely used in the British Isles and other countries show considerable variability between the labelled and assayed potencies.[10]

In view of such findings, interested workers in antibiotics in other countries should be encouraged to question the reliability of the discs of local manufacture and insist on suitable authoritative controls. If this can be accomplished in the relatively few countries in which discs are manufactured, international standardization of antibiotic sensitivity discs should soon follow, since many of these manufactured discs have distribution unlimited by national boundaries. Then, ultimately, would standardization of sensitivity methods be accomplished. The obvious practical result would be that comparable figures for degrees of bacterial resistance would be available, and the term "resistant" strain would always mean the same.

## RECOMMENDATIONS

Laboratories can and should control every detail of their method of sensitivity testing, regardless of type. However, if they use commercial discs, these too must be standardized.

If standardization of antibiotic sensitivity discs and ultimately of all sensitivity methods is to be accomplished, an international meeting of interested workers in the antibiotic field should be organized with the object of reaching agreement on regulations concerning methods of antibiotic sensitivity testing.

## SUMMARY

The value of the antibiotic sensitivity tests to the clinician, and the reasons for their being in greater demand, are reviewed.

The role of the hospital laboratory and the manufacturer of antibiotic sensitivity discs in producing reliable tests is discussed.

The requirements for discs sold in Canada and the United States are outlined, as well as the need for investigation of methods and similar controls in other countries.

Some aspects of the international standardization of sensitivity discs, and ultimately of sensitivity methods, are discussed. Recommendations concerning this are made.

REFERENCES

1. HOFFMAN, R. V., JR., JACKSON, G. G. AND TURNER, M. P.: *J. Lab. & Clin. Med.*, 51: 873, 1958.
2. POWER, E. E.: *Canad. J. M. Techn.*, 17: 2, 1955.
3. BRANCH, A., STARKEY, D. H. AND POWER, E. E.: *Antibiotics Annual*, 1958-1959, 823.
4. *Idem*: *Ibid.*, 1958-1959, 833.
5. BRANCH, A. *et al.*: *Ibid.*, 1956-1957, 898.
6. GREENBERG, L., FITZPATRICK, K. M. AND BRANCH, A.: *Canad. M. A. J.*, 76: 194, 1957.
7. BRANCH, A., STARKEY, D. H. AND POWER, E. E.: *Antibiotics Annual*, 1957-1958, 107.
8. GREENBERG, L. AND FITZPATRICK, K. M.: *Canad. M. A. J.*, 79: 383, 1958.
9. WELCH, H. *et al.*: The results of a survey made by the Food and Drug Administration with commercial batches of antibiotic diagnostic discs and tablets; the assay and control of antibiotic sensitivity discs. Release by the Department of Health, Education, and Welfare, Food and Drug Administration, Washington, D.C., June 4, 1958.
10. SLEIGH, J. D.: *Scottish M. J.*, 3: 454, 1958.

RÉSUMÉ

Les antibiogrammes gagnent de l'importance aux yeux du clinicien et c'est pourquoi leur emploi augmente chaque jour. Les hôpitaux et les producteurs de disques antibiotiques employés dans ces tests ont des responsabilités bien déterminées à l'égard du degré de précision que doit atteindre cette épreuve. Les disques vendus au Canada et aux Etats-Unis sont soumis à certaines exigences exposées dans le texte. Il serait opportun que les producteurs des autres pays se soumettent à un contrôle semblable afin d'obtenir un degré d'uniformité. Les auteurs terminent en offrant quelques recommandations à l'égard d'une standardisation internationale des disques de sensibilité et, finalement, des méthodes d'usage de ces disques.

## ALLERGY IN CANADA*

C. H. A. WALTON, M.Sc., M.D.,†
*Winnipeg, Man.*

ALLERGY IN CANADA is of course much like that found elsewhere in the world, and particularly in the United States of America. It is modified by the varying flora in the several sections of the country, the climate, latitude and terrain, and by the various occupations of the people. The population of Canada is very mixed and of many origins. Generally there seems to be no difference, allergically, among the many racial groups.

The climate in general is temperate and, except on the Pacific and Atlantic Coast, varies from subzero (Fahrenheit) in winter to very hot in midsummer. The cold winters cause people to live in tightly closed centrally heated houses for six to seven months each year. These conditions perhaps account for the heavy incidence of house dust sensitivity (and other environmentals such as animal dust). Such confined living combined with a highly mobile population also leads to frequent waves of respiratory infections which pose a serious threat to infectious asthmatics.

Pollen allergy is widespread in Canada and presents an important problem, both in the number of patients and in the severity of symptoms. Pollen causes typical hay fever, pollen asthma, dermatitis and occasionally urticaria. There are three typical pollen seasons. The first, due to deciduous tree pollen, starts in April, varying in time with the latitude and the weather and rarely extending beyond the end of May except in more northerly regions. The most common offenders are from the poplar family, the elms (very commonly planted in cities and towns), the maple, the ash and the oak. In different regions of Canada one or other type predominates. On the prairies trees are relatively uncommon, except in the cities, and present no problem. The tree allergy season is short, usually about five weeks, but is intense and may cause very severe symptoms. Probably the number of cases of tree pollinosis is less than for grass or weed pollinosis.

Grass pollinosis is common throughout the populated areas, and its season usually extends from late in May to mid-July, although some scattered and less abundant species pollinate all summer and may account for a few late summer cases. The grasses occur freely in all cultivated areas, and those which are most prevalent include the blue grasses (Poa), timothy (Phleum), red top (Agrostis) and brome grass (Bromus). Clinically the problem varies greatly each year with the abundance of airborne pollen which is, of course, related to weather conditions. Frequent rain may cause a huge growth of grass, but the moisture causes the thin coated grass pollens to swell, fall and disintegrate. Plantain is widespread across Canada. Much of it is the common plantain (*Plantago major*) which produces very little pollen and is unimportant clinically. The English plantain (*Plantago lanceolata*) occurs in some areas in eastern Canada and may present local problems in midsummer.

The most important pollen problem in Canada is that due to weeds. It is very common in the large populous eastern or central provinces of Ontario and Quebec, i.e. in the region of the lower Great Lakes and upper St. Lawrence River. In the lower St. Lawrence region and in the Atlantic provinces the problem is much less, but appears to

*Summary of a paper read at the Symposium on Regional Allergy at 3rd Inter-Congress of Allergology, Paris, October 1958.

†Associate Professor of Medicine, University of Manitoba; Chief of the Division of Medicine and the Department of Allergy, Winnipeg Clinic.

Canad. M. A. J.
Aug. 1, 1959, vol. 81

be increasing. West of the Great Lakes, the weed problem is increasing as weed growth extends northward from the north-central United States, but decreases as one proceeds westward and is almost non-existent west of the Rocky Mountains.

The most important weeds are the ragweeds (species include *Ambrosia elatior, Ambrosia trifida* and *Ambrosia psilostachya*) as well as the marsh elders (*Iva xanthifolia* and *Iva ciliata*) and the cocklebur (Xanthium spp.). This group of weeds is the chief source of trouble in Ontario and Quebec and is important in Manitoba. It is rare in the western prairie provinces of Saskatchewan and Alberta, and absent from the Pacific Coast province of British Columbia. The sages (Artemisia spp.) occur chiefly in the prairie region and are important, but the most common and frequent offender in this region is Russian thistle (*Salsola pestifer*), which in dry years is a major source of trouble.

Weed control has made little headway, and as the country is opened up with roads and development of great areas of population the weed problem increases. The ragweeds have marched westward from Winnipeg nearly 300 miles in a generation, and the march appears to be continuing. Regions such as Port Arthur and Fort William at the western end of Lake Superior, once hay fever refuges, are now invaded. The Russian thistle, accidentally imported into the central plains area of the United States, has now spread northward into Canada where it became exceedingly abundant in the drought years of the 1930's.

Mould spores are very plentiful in the air throughout the country. The common saprophytes, Alternaria, Hormodendrum, and Helminthosporium, occur widely in the warmer months, appearing as soon as the snow leaves the ground and disappearing with the first snow blanket. There is also a wide group of spores occurring with little seasonal variation throughout the year including Penicillium, the yeasts, Rhizopus, Monilia, etc. Clinical sensitivity is common, particularly in the prairie provinces. It undoubtedly accounts for the many cases of known hay fever in which symptoms start before the frost destroys the weeds and in which trouble continues until snow comes in November or December.

In agricultural areas, most notably the Great Plains, pathogenic fungus spores such as rust, smut and bunt are very common, varying in abundance each year and having a season of about four weeks. While these spores are quite allergenic, as shown first by Cadham in 1923 and later proven by Wittich in 1937, our experience indicates that less than 10% of the rural allergic population are affected and the problem is a relatively minor one, clinically.

Industrial dusts are of course a very important source of allergy. Perhaps the most serious of these is grain dust. This term is a very general one, but as in the case of house dust, it is remarkably uniform allergenically. Various things in grain dust have been suspect, such as saprophytic and pathogenic mould spores, but the dust itself seems to be intrinsically allergenic. This is borne out by the fact that the crushing of grain, as for feed or milling, greatly enhances its allergenicity. There is a distinct variation in the dusts from wheat, barley, rye and oats, but only in degree, and generally sensitivity to one implies sensitivity to all. Grain dust allergy causes rhinitis, asthma and a particularly severe form of atopic dermatitis. It is a serious problem to farmers and to those engaged in the grain trade. It is also an important problem near the great shipping grain terminals and mills, and citizens of such cities as Fort William and Port Arthur at the head of the Great Lakes often suffer from it, even if not engaged in any way in the grain trade. Farmers, of course, also suffer commonly from sensitivity to animal and poultry dust. Animals create important environmental problems in homes.

Furriers and those engaged in the great fur trade often suffer from respiratory and skin allergy. Other industries also present problems to the allergic sufferer, and among these I might mention the pulp and paper factories and the smelters, both of which produce highly irritant if not allergic gases. Smog is an uncommon phenomenon in Canada.

Food allergy is relatively common and presents no unusual features. Fish sensitivity is probably more common in the Maritimes. Owing to a highly organized and extensive distribution system, most of the population has a highly varied diet and there are few notable seasonal or special food problems. Drug sensitivity is becoming more common, or more frequently recognized, and differs little from that seen elsewhere. Penicillin, sulfonamides and aspirin continue as major drug allergens.

In Canada, it is probable that about 60% of respiratory allergy is due to inhaled and environmental allergens or food. The remainder, the so-called intrinsic cases, have a high degree of infectious factors.

The population is becoming highly conscious of allergy, and this probably reflects the popular situation in the U.S.A. Multiple cases in families are common and many people are becoming aware of the hereditary and environmental problems involved. Lay interest in allergy seems at times to be ahead of that of the general medical profession.

There is a disturbing tendency among physicians for too frequent use of corticosteroids in allergic cases without adequate effort at simpler and safer management. This probably reflects a lack of experienced allergists in the country and a rather uniform neglect of the subject in undergraduate medical education. Fortunately, more and more systematic teaching of allergy to medical students is appearing; in at least half of our medical schools some formal instruction is now being given, and it is expected that more will gradually follow this path.

Much of Canada has been carefully surveyed for airborne allergens and more will be done. The relationship of climate to allergic disease is often still obscure, although climate is too often blamed for a change in the patient's condition when a more rational explanation can be found in his immediate environment. The farmer who is benefited by moving to the warmer but damper sea level region of the Pacific Coast may only be responding to his removal from grain or animal dust or weed pollen. Basic research into the fundamental processes of allergy and in respiratory physiology is going forward in several Canadian universities and clinical studies are also continuing in various centres. It is hoped that with improving undergraduate and graduate education and with continually advancing knowledge the management of allergic disease in Canada will continue to improve.

RÉSUMÉ

L'allergie au Canada est liée au problème que présentent des hivers longs et rigoureux avec l'atmosphère chaude et sèche des habitations ainsi que les différents pollens libérés du printemps à l'automne. Il existe trois saisons de pollination, à savoir: celle des arbres à feuilles caduques, d'avril à mai, comprenant les ormes, les érables, les frênes et les chênes; celle des herbes, de mai à la mi-juillet, comprenant le pâturin (*Poa*), la fléole des prés (*Phleum*), l'agrostide stolonifère et les bromes, et enfin, celle des mauvaises herbes, d'août à octobre, comprenant les ambrosies (surtout la Grande Herbe à poux), les ives (*I. xanthifolia* et *ciliata*), la lampourde piquante (*Xanthium*) et la soude roulante (*Salsola pestifer*). Les spores de moisissures contribuent à compliquer la situation, de la fonte des neiges au retour de l'hiver. Chaque région possède ses problèmes particuliers qui varient selon le climat, la géographie et la flore. Les poussières industrielles comme celles des céréales forment également une source d'allergie très importante. De même que dans les autres pays certains aliments et médicaments peuvent aussi être en cause.

Winnipeg Clinic, St. Mary's & Vaughan St.,
Winnipeg, Manitoba.

# Case Reports

## MALIGNANT MESENCHYMOMA (HÆMANGIOBLASTOMYXOMATOUS VARIETY) IN A FIVE-YEAR-OLD BOY*

G. F. KIPKIE, M.D. and
M. DARIA HAUST, M.D., *Kingston, Ont.*

MESENCHYMOMA is a term which has been in use for a relatively short time. This term was coined by Gilmour[4] in 1943 to indicate that the tumour consists of two or more components derived from mesenchyme. While the benign varieties of this tumour occur most commonly in the urogenital tract[11] and less commonly in the muscles and subcutaneous tissue,[10] the malignant variety, although frequently encountered in the urogenital tract[7] and breast,[10] can be found anywhere in the body.

The criteria for malignant mesenchymoma are fulfilled when the tumour is composed of two or more cell types, each type being malignant. Each type of tissue is derived from primitive mesenchyme, and none of these components "can be fitted into the standard recognized varieties of sarcoma, and each one would have to receive a different compound name if they were to be designated by a term recording all of the component parts".[10]

It is not in the scope of this communication to review the subject of malignant mesenchymoma, since this has been done recently and comprehensively by several authors.[7, 8, 10] The purpose of this publication is to report on a case of malignant mesenchymoma of a hæmangioblastomyxomatous type, a rather rare variety. An attempt will be made to arrive at some conclusion as to its histogenesis and pathogenesis, by means of a careful morphological study.

*Clinical summary.*—A five-year-old boy, M.L., was admitted on August 4, 1957, to the Kingston General Hospital with a six-week history of a swollen area at the angle of the mandible on the left side. Further history revealed that he was well until November 1956, at which time he developed what was thought by his parents to be measles, since his older sister had just recovered from this infection. There was, however, no medical confirmation of this diagnosis. The rash lasted four to five days; he had a slight fever and a slight cough at that time. The boy did not regain his appetite. In April 1957, he was seen by an ear, nose and throat specialist, because of soreness of the left ear. The temperature was not elevated. The patient was treated with antibiotics, and the soreness disappeared only to return when the treatment was stopped. The antibiotics were readministered and the improvment lasted this time only for a few days. He became listless and tired, and refused to play. He was then seen in the out-patient department of the Kingston General Hospital, in May 1957, where it was noticed that the mesenteric lymph nodes were enlarged. He responded to antibiotics for a short period only. The lymph nodes disappeared, but since the tiredness and listlessness returned, he was admitted to the hospital on June 8 for investigation. Two days after admission, his left parotid region was noted to be swollen but all tests performed were negative. He was sent home when the diagnosis of mumps was made. Since the swelling still persisted five weeks later, enlarging at night, and the child suddenly developed a left-sided strabismus, he was admitted on August 4, 1957, to Kingston General Hospital. The functional enquiry revealed that the child had recently suffered from nightly headaches, lasting for 10 to 15 minutes and located in the central frontal area. On examination, the significant finding was the stony hard mass on the left side of the face over the parotid area. It was slightly tender, smooth and regular. On the inside of the mouth there was a suggestion of a swelling in the left side of the posterior

*From the Departments of Pathology, Queen's University and the Kingston General Hospital, Kingston, Ontario.
Presented in part at the Fifty-fifth Annual Meeting of the American Association of Pathologists and Bacteriologists, Cleveland, Ohio, April 24-26, 1958.

Canad. M. A. J.
Aug. 1, 1959, vol. 81

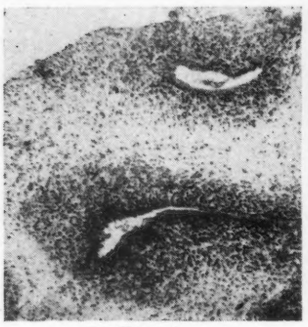


Fig. 1

Fig. 2

Fig. 1.—Tumour consists of two distinct components, a vascular and a myxomatous (light grey in photograph). Hæmalum-phloxine-saffron; × 31.

Fig. 2.—Another area of tumour showing the predominantly myxomatous components (slightly basophilic in the section, light grey in photograph). A few delicate connective tissue fibres (yellow in slide, darker grey in photograph) and a few cells are seen scattered throughout the loose tissue. Hæmalum-phloxine-saffron; × 31.

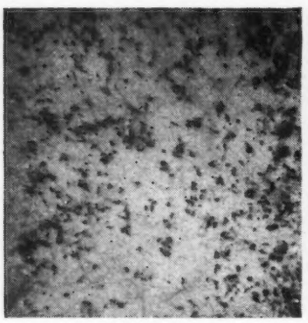


Fig. 3

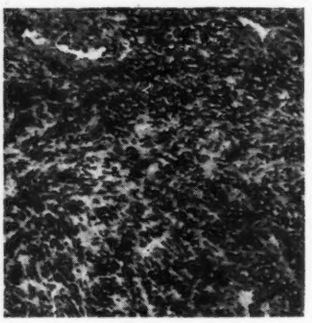


Fig. 4

Fig. 3.—Higher magnification of Fig. 2 shows that the cellular elements in the myxomatous component are stellate and bizarre. In this section the loose matrix (light grey in photograph) gave a positive staining reaction with Alcian blue (blue in section). Alcian blue-PAS-hæmatoxylin-orange G; × 102.

Fig. 4.—The vascular component is seen to consist of a few larger and numerous small channels. In addition, innumerable clumps of cells are present. Hæmalum-phloxine-saffron; × 102.

wall of the pharynx. There was a left sixth nerve paralysis and, in view of the absence of any signs of central nervous system disease, it was considered that this represented direct tumour invasion, probably of the temporal bone. An x-ray examination revealed considerable destruction of the ramus of the left mandible by a large, soft tissue mass.

Biopsy was carried out on August 10, and at operation the x-ray findings were confirmed, in that the ramus of the mandible appeared to have been completely destroyed and replaced by soft, greyish-white tumour tissue.

*Microscopic examination.*—The tumour was composed of two distinctive types of tissue (Fig. 1). The one was predominantly a loose myxomatous matrix (Fig. 2) containing scanty cellular elements of bizarre, star-like shape, similar to myxoblasts. This loose myxomatous matrix gave a positive staining reaction with Alcian blue (Fig. 3), thus indicating an acid mucopolysaccharide-rich stroma. Embedded in this intercellular substance was the other component of the tumour. It consisted of numerous vascular channels varying in size and content (Fig. 4). Some of these channels contained blood; others contained for the most part faintly eosinophilic, protein-rich fluid. A remarkable feature of these vascular spaces was the uniform absence of a well-developed vessel wall, the latter consisting only of an endothelial lining and occasionally of some dense connective tissue fibres, without formation, however, of a complete basement

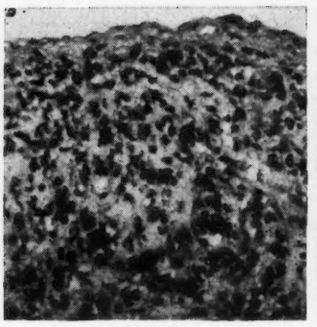


Fig. 5

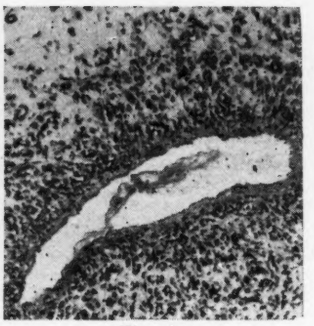


Fig. 6

Fig. 5.—The vascular lumen (top in photograph) is limited by a wall which consists of only a few strands of connective tissue (dark grey in photograph, yellow in slide) lined incompletely by endothelial cells. Hæmalum-phloxine-saffron; × 244.

Fig. 6.—Radiating from a larger vascular channel are single and groups of cells having a dense chromatin mass. Their number decreases away from the "main" lumen as the myxomatous matrix increases in volume. Hæmalum-phloxine-saffron; × 102.

membrane (Fig. 5). Surrounding these vascular channels were "cells", which were most abundant in the immediate vicinity of the larger vascular spaces and which decreased gradually in number the greater the distance from the vascular space (Fig. 6). These "cells" were of two varieties. They were either small with a single nucleus and consistently containing a "vacuole", or they appeared to be of the giant cell type. In the small cells, it was difficult to determine where this "vacuole" was situated. At times it seemed as if it were within cytoplasm pushing the nucleus eccentrically, but it was also seen at times to be within the nuclear mass. However, here too the main mass of chromatin was pushed aside, leaving only a rim of the chromatin substance enclosing the "vacuole" from the opposite side (Fig. 7). On the other hand, the large formations which created at first the impression of being giant cells were composed of deeply eosinophilic cytoplasm and nuclear masses always placed at the very periphery. It was unusual in that the chromatin masses were pushed to such an extreme position at the periphery as to give the impression of being situated distinctly outside the cytoplasm (Fig. 8). Also, on closer examination, the "cytoplasm" of some of these "giant cells" was not homogeneous but seemed to be composed of closely packed, round small corpuscles. It was for this reason that we thought we were dealing with vascular channels rather than giant cells. Special stains confirmed this impression. Silver-positive reti-

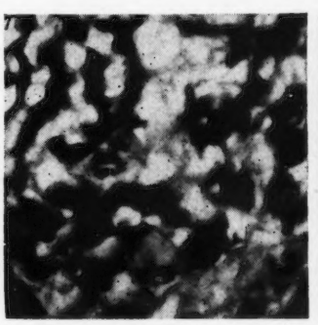


Fig. 7

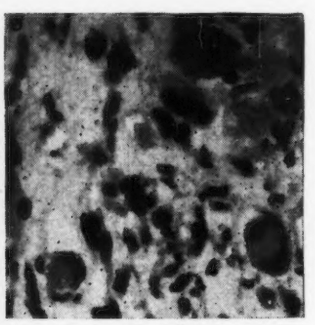


Fig. 8

Fig. 7.—A higher magnification of the cellular component of Fig. 6 discloses the presence of numerous "vacuoles" within the cytoplasm as well as in the nuclei. Note the dense, bizarre chromatin masses. Hæmalum-phloxine-saffron; × 780.

Fig. 8.—Some of the cells have the appearance of giant cells with intensely eosinophilic cytoplasm (dark grey in photograph, red in slide) and numerous dense nuclei which are placed eccentrically. One of these giant cells (upper half of the photograph) has three small "vacuoles" in its cytoplasm. Hæmalum-phloxine-saffron; × 410.

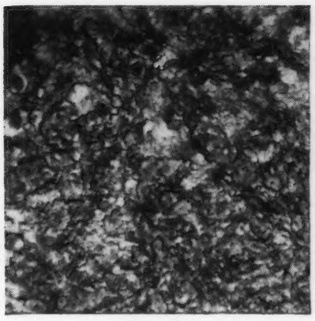


Fig. 9

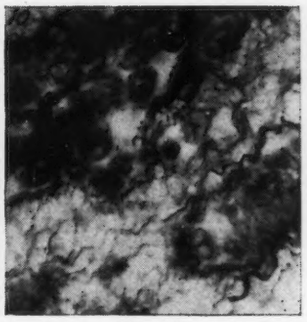


Fig. 10

**Fig. 9.**—The tissue is rich in silver-positive coarse and delicate reticulum fibres, many of which outline the "giant cells" shown in **Fig. 8.** Foot's modification of Hortega's silver carbonate method; × 244.

**Fig. 10.**—Higher magnification of **Fig. 9** shows that the giant cells are in reality vascular spaces. Two red blood corpuscles are seen in a channel in the right lower corner. Foot's modification of Hortega's silver carbonate method; × 972.

culum fibres outlined these vascular spaces (Fig. 9), thought previously to be giant cells. At a higher magnification (Fig. 10) it could be seen that these vascular spaces surrounded by black, silver-positive reticulum fibres contained red blood cells in a few areas. When stained with Alcian blue-PAS (periodic acid-Schiff)-hæmatoxylin-orange G, these vascular spaces were outlined by an incomplete PAS-positive basement membrane, and the content, which seemed to be homogeneous in routine stains, proved in many areas to be small round corpuscles. These stained a deep yellowish-orange, similar to the staining of red blood cells with this technique (Fig. 11). The eccentric clumps of chromatin proved to be the nuclei of very anaplastic lining cells of the vascular spaces. Some of the vascular channels contained no red blood cells but a homogeneous, proteinous material. No nucleoli and only an occasional mitotic figure could be seen. A few areas of necrosis and hæmorrhage were present in the loose, myxomatous stroma.

In trying to establish the mode of the development of these vessels, we were able to trace the primitive lumina to their early stage of formation. A primitive mesenchymal cell nucleus (? mesenchymal cell) (Fig. 12) appears to curve on itself. It thins out and the thinned ends of chromatin meet, thus enclosing the previously ill-defined cytoplasm of the mesenchymal cell. Presumably this enclosed cytoplasm liquefied, forming a primitive channel which at times was filled with primitive blood plasma. An alternative way by which the vessels form was seen where several of the primitive mesenchymal cells (mesenchymal angioblasts) conglomerated to form a "giant cell" (Fig. 8). Here the central eosinophilic portion was liquefied gradually and this resulted in the formation of a tube filled with liquefied proteinous material. Just how these primitive channels abutted to produced a continuous vessel could not be seen in this study.

The nature of the numerous "vacuoles" was apparent from these observations. They represented different stages of liquefaction either in a single cell or in a giant cell, as described above.

Since the study showed the tumour to be composed of two unrelated constituents (hæmangioblastomatous and myxomatous) derived from primitive mesenchyme, and since both components exhibited malignant properties, it seemed appropriate to apply the name malignant mesenchymoma.

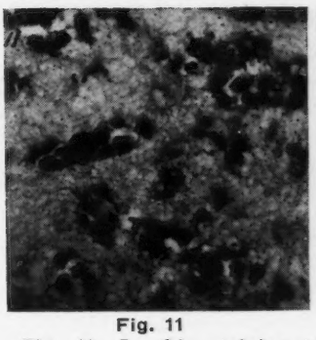


Fig. 11

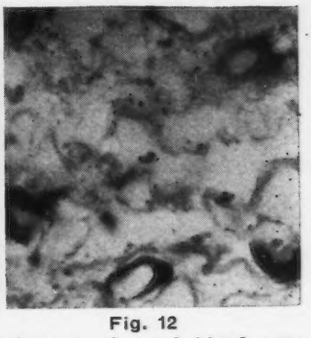


Fig. 12

**Fig. 11.**—In this staining technique, the red blood corpuscles are stained very brightly (deep yellowish-orange in slide, black in the photograph). They are seen in vascular channels partly outlined by a PAS-positive material (purplish-red in slide, dark grey in photograph). Alcian blue-PAS-hæmatoxylin-orange G; × 410.

**Fig. 12.**—A mesenchymal angioblast having a plump, abundant chromatin mass and a scanty, ill-defined cytoplasm is seen in the right lower corner curving slightly. This curving around its own axis is seen more advanced in the cell to the extreme left and seems to be completed with closure of a thin chromatin rim in the cell on the top of the photograph. The cytoplasm of this cell is dark grey and completely embraced by chromatin mass, which is more abundant to the right. Finally, the cytoplasm becomes completely liquefied, giving rise to a small lumen as seen in the bottom, centre. Alcian blue-PAS-hæmatoxylin-orange G; × 1460.

The child died at home five months from the onset of symptoms. Unfortunately an autopsy was not performed.

## DISCUSSION

Both the benign and malignant variety of mesenchymal tumours are not confined only to the urogenital tract[7, 11] and the mammary gland[10] but can occur almost anywhere in the body,[2, 5, 8, 12] where both derivatives of the mesenchyme, whether somatic or visceral mesoderm, occur.[6]

A very attractive theory as to the origin of the blood channels is offered by Gloggengiesser[5] and Mollier (in Gloggengiesser, 1939).[5] They feel that there are two possibilities of origin for any blood vessel forming in extrauterine life: either from "leftover" reticulum (i.e., dysontogenetic) or from a pre-existing endothelium which has the ability (and potentiality) to "convert" itself into an undifferentiated reticulum which in turn forms not only blood vessels but also blood corpuscles, connective tissue, etc. Although these authors do not define the term "reticulum", one is certain that this term is in their usage synonymous with undifferentiated (primitive) mesenchyme.

A recent report on a malignant mesenchymoma arising in the scar of a thermal burn[3] might indicate that the origin of these tumours is not necessarily dysontogenetic as indicated by McFarland[7] but that they arise in the course of regeneration which follows severe injury. In our case, however, it would appear that the age of the patient and the fact that he was born of elderly parents (approx. 55-60 years of age), favour a dysontogenetic origin.

The morphological appearance of the tumour in our case is similar to that in the case reported by Donovan and Santulli,[2] in one of the cases reported by Gilmour[4] and in Case 29 in the series reported by Changus, Speed and Stewart,[1] even though the latter authors preferred to call their

Canad. M. A. J.
Aug. 1, 1959, vol. 81

tumour a malignant angioblastoma rather than a malignant mesenchymoma. They maintain that the myxomatous component in the tumour is the end stage of degenerating neoplastic angioblasts. However, we feel that the abundant myxomatous tissue with numerous myxoblasts present is an equal and separate component (Figs. 1, 2 and 3) rather than a product of degeneration.

In accordance with Sabin[9] we were able to trace the formation of vascular channels either within a single cell (mesenchymal angioblast) (Fig. 12) or in a group of cells where the nuclei were placed at the periphery of the clump (Fig. 8). Blood plasma and red blood corpuscles could be seen in these newly formed channels.

SUMMARY

A case of a malignant mesenchymoma in a 5-year-old boy is described. It grew rapidly in the left mandibular region, destroying the ramus and causing death five months after its onset. It consisted of a hæmangioblastomatous and a myxomatous component, both exhibiting malignant properties, and was most probably dysontogenetic in origin. Detailed histogenesis of the hæmangioblastomatous component is described and discussed.

We should like to thank Dr. D. L. C. Bingham, Professor and Head of the Department of Surgery, and Dr. A. M. Bryans, Assistant Professor of Pædiatrics, for their kind permission to publish this case.

REFERENCES

1. CHANGUS, G. W., SPEED, J. S. AND STEWART, F. W.: *Cancer*, 10: 540, 1957.
2. DONOVAN, E. J. AND SANTULLI, T. V.: *Ann. Surg.*, 124: 90, 1946.
3. GAYNOR, W. B. AND DELASHMUTT, R. E.: *Am. J. Clin. Path.*, 28: 74, 1957.
4. GILMOUR, G. R.: *J. Path. & Bact.*, 55: 495, 1943.
5. GLOGGENGIESSER, W.: *Beitr. z. path. Anat. u.z. allg. Path.*, 103: 256, 1939.
6. HUECK, W.: *Ibid.*, 103: 308, 1939.
7. MCFARLAND, J.: *Surg. Gynec. & Obst.*, 61: 42, 1935.
8. RABSON, S. M.: *Arch. Path.*, 25: 185, 1938.
9. SABIN, F. R.: *Carnegie Inst., Pub. No. 272, Contribut. Embryol. Wash.*, 9: 213, 1920.
10. STOUT, A. P.: *Ann. Surg.*, 127: 278, 1948.
11. TAKACS, F.: *Virchow's Arch. f. path. Anat.*, 309: 550, 1942.
12. HYDE, W. R., WHITE, J. E. AND STOUT, A. P.: *Cancer*, 3: 653, 1950.

## THECA CELL TUMOUR OF THE OVARY

J. S. BARR, M.B., Ch.B., M.R.C.O.G.,*
*Edmonton, Alta.* and
J. MACVICAR, M.B., Ch.B., M.R.C.O.G.,†
*Glasgow, Scotland*

THE OVARIAN theca cell tumour or thecoma is a relatively rare neoplasm, just over 150 having been recorded since the original description by Löffler and Priesel[1] 27 years ago. The thecoma is closely related in histogenesis to the granulosa cell tumour; and elements of the one type of cell may be found in what is predominantly a tumour of the other cell type. This mixing of thecal and granulosa cells undoubtedly accounts for the varying estimates of incidence found in the literature on thecoma.[2, 3]


Fig. 1.—Portion of specimen removed at operation showing ovary with theca cell tumour (Case 1).

Tumours reported vary from a few millimetres in diameter to large neoplasms of considerable size.[4, 5] They are rarely bilateral.

Malignancy is less common than in granulosa cell tumours and occurs in about 3 per cent of thecomas.[6] Despite an innocent histological appearance, there is some risk of recurrence and metastasis even many years after apparent complete surgical removal.[7]

Thecoma has been found in females of all ages from one year[8] upwards, but the majority occur in post-menopausal women, in whom they typically produce evidence of œstrogen production in the form of post-menopausal bleeding. In children the tumour may cause the onset of precocious pseudopuberty. During the reproductive years there may be alteration in the menstrual cycle such as one would associate with an excess of œstrogen. The tumours have been reported during pregnancy.[9, 10]

Despite the usual occurrence of œstrogenic effects, Shippel[11, 12] has published evidence of androgen production by the theca cell, and patients showing signs of virilism have been reported.[13]

Endometrial carcinoma may accompany an ovarian œstrogenic tumour, and Novak[14] found this more frequently with thecoma. Benign endometrial hyperplasia is common, but the histological pattern can be so atypical that differentiation from carcinoma is far from easy.

Although thecoma is a rare cause of post-menopausal bleeding,[15] one of the authors (J.S.B.) has had personal knowledge of three such patients.

*Honorary Sessional Instructor, Department of Obstetrics and Gynæcology, University of Alberta, Edmonton.
†Senior Registrar, Department of Obstetrics and Gynæcology, Stobhill General Hospital, Glasgow, Scotland.

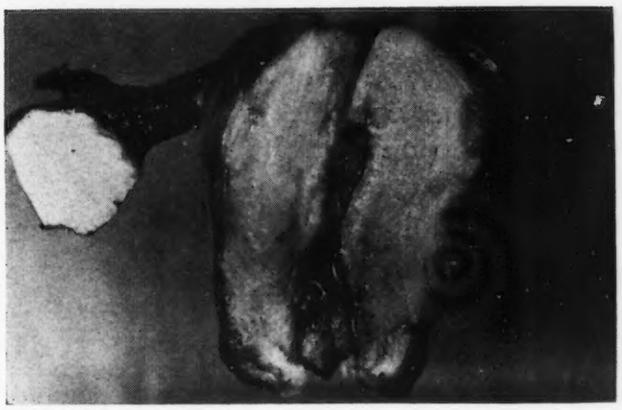


Fig. 2.—Operation specimen from Case 3, showing theca cell tumour of the ovary. Endometrial and myometrial thickening is also evident.

CASE 1.—A 55-year-old woman, para 2, complained of three days' bleeding in December 1953. The menopause had occurred seven years previously. The bleeding was similar in amount to her normal menstrual loss but several small clots had been passed. She had no further complaints but admitted to occasional brownish vaginal discharge since the menopause.

She was a healthy woman with no abnormality on general physical examination. The blood pressure was 140/100 mm. Hg and the hæmoglobin value 12 g. per 100 ml. Vaginal examination revealed a uterus slightly bulky for her age but no other obvious pelvic abnormality.

Total hysterectomy and bilateral salpingo-oophorectomy were performed without preliminary curettage.

*Pathological report.*—The uterus was 9 cm. long and contained an endometrial polyp 3.5 cm. in length. The left ovary was atrophic and the right contained a cream-coloured tumour occupying more than half its substance.

*Histology.*—The endometrium was thin and non-secretory, with hyperplastic changes in the glands. The endometrial polyp consisted of a fibrosed stroma with hyperplastic glandular epithelium. Hæmorrhagic congestion was present at the tip of the polyp. The right ovary showed a thecoma with a margin of hyaline tissue and formed of interlacing spindle-shaped cells and hyaline deposits.

The patient had an uneventful convalescence. Vaginal smears taken a few days after operation showed considerable glycogen staining and eosinophilia in a rather basal type of cell. Smears taken six weeks later showed much less glycogen activity. It was possible to follow up this case for two years, and during this time she remained well, with no evidence of tumour recurrence.

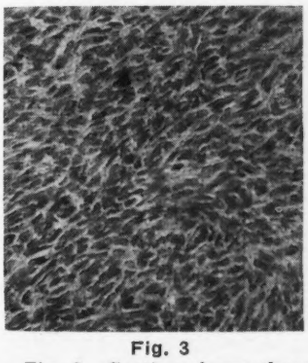


Fig. 3

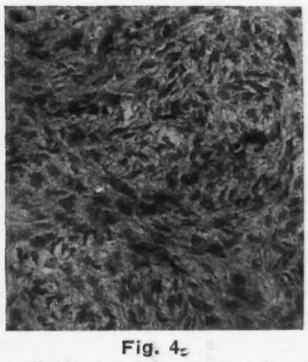


Fig. 4

Fig. 3.—Section shows theca cells in ovarian tumour from Case 1. Hæmalum and eosin; × 250.

Fig. 4.—Section shows theca cells in ovarian tumour from Case 2. Hæmalum and eosin; × 250.

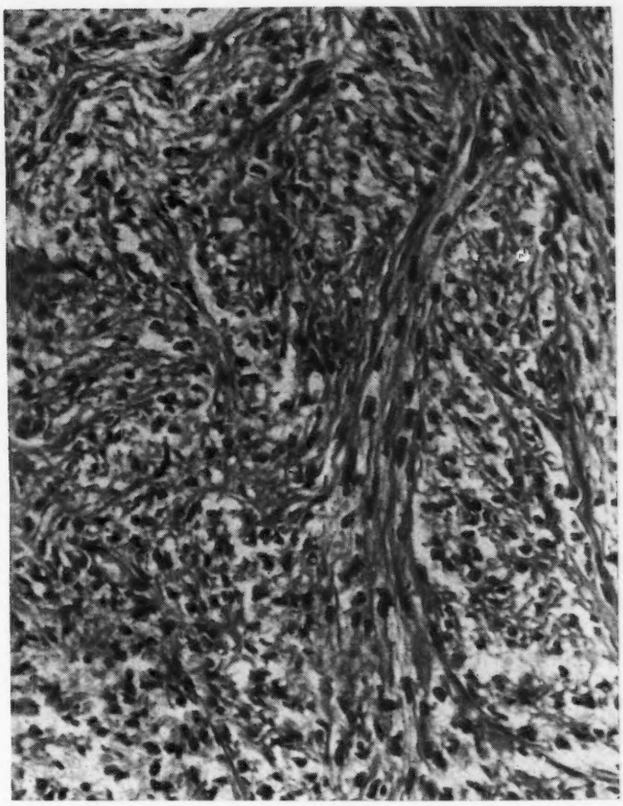


Fig. 5.—Section from ovarian tumour of Case 3, showing bundles of theca cells among bands of connective tissue. Hæmalum and eosin; × 250.

CASE 2.—A 53-year-old woman presented in August 1955, complaining of three months' post-menopausal bleeding. She was gravida 2, one pregnancy having ended in a six-month abortion and the other in a tubal pregnancy. The menopause had occurred two years previously, and six months later she began to have a brown vaginal discharge, gradually increasing in amount until frank bleeding was occurring three months before her admission. The bleeding had been continuous but never heavy.

She looked healthy, and no abnormality was noted on general examination. Her blood pressure was 130/80 mm. Hg and the hæmoglobin value was 10.5 g. per 100 ml. Pelvic examination revealed a normal-sized uterus, and a cystic mass 7 to 10 cm. in diameter was felt through the right fornix. Laparotomy exposed a semi-solid, yellowish right ovarian cyst. The uterus, right tube and both ovaries were removed.

*Pathological report.*—The uterus and left ovary were normal. The right ovary was replaced by a solid tumour, 7.5 cm. in diameter and consisting of orange-yellow tissue within a thin capsule.

*Histology.*—The endometrium was atrophic, with a few dilated glands. The ovarian tumour was a fibrous type of thecoma with a thin capsule of normal ovarian tissue.

The patient made an uneventful recovery. Two weeks after operation she complained of occasional hot flushes, and these disappeared during the next two

Canad. M. A. J.
Aug. 1, 1959, vol. 81

months without treatment. When last seen one year after operation, she was in good health and no abnormality was noted on pelvic examination.

These two patients were seen in the department of obstetrics and gynæcology, Stobhill General Hospital, Glasgow. The third patient was referred from the Alberta Cancer Clinic, Edmonton.

CASE 3.—This patient, aged 60 and para 10, had her last menstrual period nine years previously. She complained of vaginal bleeding for eight months, intermittent at first but continuous for three months and increasing in amount. She had recently lost 8 lb. in weight.

She was an obese woman with a blood pressure of 160/90 mm. Hg and a hæmoglobin value of 10 g. per 100 ml. Pelvic examination was difficult owing to her obesity but the uterus was felt to be considerably enlarged and soft.

On November 7, 1958, fractional curettage and cervical biopsy were performed and large quantities of friable-looking material were obtained from the uterine cavity. These curettings showed endometrial hyperplasia and cystic glandular dilation but no malignant changes.

A week later, total hysterectomy and bilateral salpingo-oophorectomy were performed. At operation the left ovary was noted to be the seat of a firm, pale yellow tumour.

*Pathological report.*—The uterus measured 11 by 8 by 6 cm. and weighed 250 g. The myometrium was considerably thickened and the cavity showed evidence of recent curettage and contained friable grey material at the fundus.

*Histology.*—The left ovary was 4 cm. in diameter and consisted of interlacing bundles of broad spindle cells separated by bands of connective tissue. Mitoses were rare. Fat stains showed fat granules scattered in the cytoplasm of some of the spindle cells and this finding suggested a diagnosis of thecoma rather than fibroma.

The patient's recovery was delayed by a ruptured abdominal wound which healed satisfactorily after resuture.

SUMMARY

Three patients are described, all of whom presented with the leading symptom of post-menopausal bleeding. In each case it appeared that this symptom was the end result of œstrogen production by an ovarian theca cell tumour.

REFERENCES

1. LÖFFLER, E. AND PRIESEL, A.: *Beitr. z. path. Anat. u.z. allg. Path.*, **90**: 199, 1932.
2. FALLS, F. H., RAGINS, A. B. AND GOLDENBERG, M.: *Am. J. Obst. & Gynec.*, **57**: 1107, 1949.
3. BANNER, E. A. AND DOCKERTY, M. B.: *Surg. Gynec. & Obst.*, **81**: 234, 1945.
4. WEINER, I. D.: *Memphis M. J.*, **25**: 44, 1950.
5. REINER, W. C.: *West. J. Surg.*, **56**: 205, 1948.
6. ROGERS, W. S., GORDON, R. E. AND MARSH, M. R.: *Am. J. Obst. & Gynec.*, **64**: 1289, 1952.
7. DIDDEL, A. W.: *Cancer (N.Y.)*, **5**: 215, 1952.
8. GORDON, V. H. AND MARVIN, H. N.: *J. Pediat.*, **39**: 133, 1951.
9. WEBB, C. F. AND GOUGH, J. A.: *Am. J. Obst. & Gynec.*, **65**: 211, 1953.
10. STERNBERG, W. H. AND GASKILL, C. H.: *Ibid.*, **59**: 575, 1950.
11. SHIPPEL, S.: *J. Obst. Gynæc. Brit. Emp.*, **57**: 362, 1950.
12. *Idem*: *Ibid.*, **62**: 321, 1955.
13. ALEXANDER, W. S. AND BERESFORD, O. D.: *Ibid.*, **60**: 252, 1953.
14. NOVAK, E.: Gynecologic and Obstetric Pathology, 3rd ed., W. B. Saunders, Philadelphia, 1952, p. 417.
15. SUTHERLAND, A. M. AND MCBRIDE, J. M.: *J. Obst. Gynæc. Brit. Emp.*, **61**: 238, 1954.

# CAVERNOUS TRANSFORMATION OF THE PORTAL VEIN IN POLYCYTHÆMIA VERA*

A. A. RITZEN, M.D.,
W. B. LEACH, M.D., M.Sc. and
D. M. WHITELAW, M.D., F.R.C.P.[C],
*Vancouver, B.C.*

POLYCYTHÆMIA vera is frequently complicated by vascular accidents. These may be hæmorrhagic or thrombotic. The cause of hæmorrhage is obscure. Low fibrinogen levels and defects of clot retraction have been demonstrated. It is possible also that mechanical distension of blood vessels and impairment of nutrition of the intima may play some part.[1] The cause of thrombosis is equally obscure. Increased number of platelets, increased viscosity of the blood and impaired nutrition of the vascular endothelium due to mechanical distension may all contribute. Clinical evidences of thrombosis are usually associated with obstruction of larger arteries in the brain, heart or intestinal tract.[2] Less frequently, venous thrombosis may be the cause of intra-abdominal complications.[3] The present case report concerns a patient with polycythæmia vera who during the course of her illness developed symptoms of portal obstruction and who at operation and autopsy was found to have cavernous transformation of the portal vein.

A 40-year-old white woman was referred to us by Dr. McMurtry of Vernon, B.C. She had first noted a painful mass in the right upper quadrant of her abdomen in 1955. The pain was worse after walking and working but not after eating. It was constantly relieved by aspirin and codeine. For five years before the onset of this pain she had noticed that a warm bath would induce burning and itching of her skin which would persist for up to 30 minutes.

There was no family history of blood disease. She had had five pregnancies of which three were stillbirths after six months' gestation. During her second pregnancy, she had one convulsion and after her last she had a moderately severe hæmorrhage. From early adolescence, she had suffered from migrainous headaches.

It was found on initial examination that her liver extended 15 cm. below the right costal margin at the lateral border of the rectus, and her spleen extended a similar distance below the left costal margin. The retinal veins were engorged. The hæmoglobin value was 16.8 g. %. The red blood cell count was 6.27 million per c.mm. The white cell count was 15,650 per c.mm. and the erythrocyte sedimentation rate was 2 mm. in one hour. Venesection performed five times over a three-month period partially relieved her pain and lowered her hæmoglobin level to 9.3 g. %.

On admission to the Vancouver General Hospital the above findings were confirmed and she was found also to have slight œdema of her lower legs. Results of liver function tests were normal. The hæmoglobin level was 11.2 g. % and the red cell count 5.4 million.

*From the Department of Pathology, Vancouver General Hospital, and the Department of Medicine, The University of British Columbia, Vancouver, B.C.

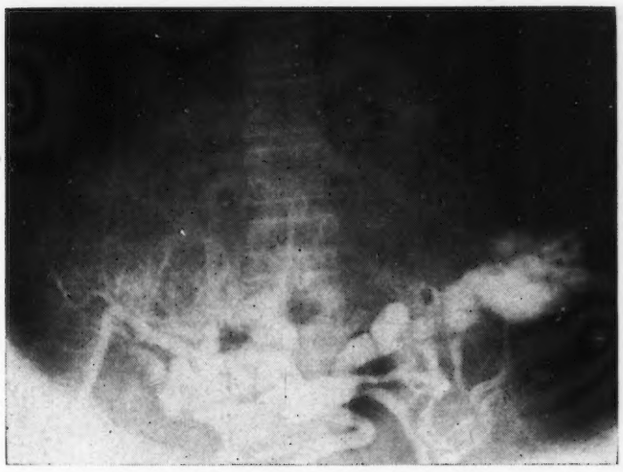


Fig. 1.—Splenoportography showing dilated collateral portal vessels. No single portal vein is evident.

The red cells were microcytic and hypochromic. The platelets numbered 780,000 per c.mm. The white blood cell count was 13,800 and the sedimentation rate was 10 mm. in one hour. The bone marrow showed increased cellularity and many megakaryocytes. The red cell mass determined with chromium$^{51}$ was 1280 ml. compared with an expected normal of 1320 ml., and the plasma volume was 3070 ml. compared with an expected normal of 1830 ml. These findings were interpreted as indicating polycythæmia with the red cell mass reduced by venesection. Splenic aspiration showed no abnormality. X-ray examination of the œsophagus, stomach and duodenum was negative. She was treated with 600 r of x-irradiation over her spleen, with some relief of discomfort.

During the next six months her hæmoglobin level rose to 12 g. % and her red cell count to 6.2 million. Her white cell count varied between 10,000 and 20,000. By October 1956, the red cell mass had risen to 1630 ml. and the plasma volume had fallen to 2060 ml. She was again treated by x-irradiation over both liver and spleen and was given iron by mouth.

For the succeeding 12 months her clinical condition was stationary and the pain, while almost constant, was bearable. Her hæmoglobin level was maintained at about 12 g. % by monthly venesections. An examination of blood and bone marrow in October 1957 was essentially unchanged. Results of blood volume studies were similar to those of a year before. X-ray examination of œsophagus, stomach and duodenum was again negative. Splenic aspiration now yielded megakaryocytes and other myeloid elements. A punch biopsy of the liver showed normal liver tissue. A cone biopsy of the cervix showed chronic cervicitis. After this procedure she bled briskly for two days.

In April 1958, she contracted an upper respiratory infection and over a period of one week her weight increased by 8 lb. accompanied by a 3 inch (7.5 cm.) increase in girth. She was found to have ascites and œdema of her lower extremities. She had no dyspnœa, cardiomegaly or increase in venous pressure. Re-examination of her blood and bone marrow showed no significant changes from those noted previously. Except for a serum globulin of 2.5 g. %, results of liver function tests were normal. She was considered to have developed a splenic or portal vein obstruction. With bed rest, salt restriction and diuretics she lost 11 lb. and felt improved.

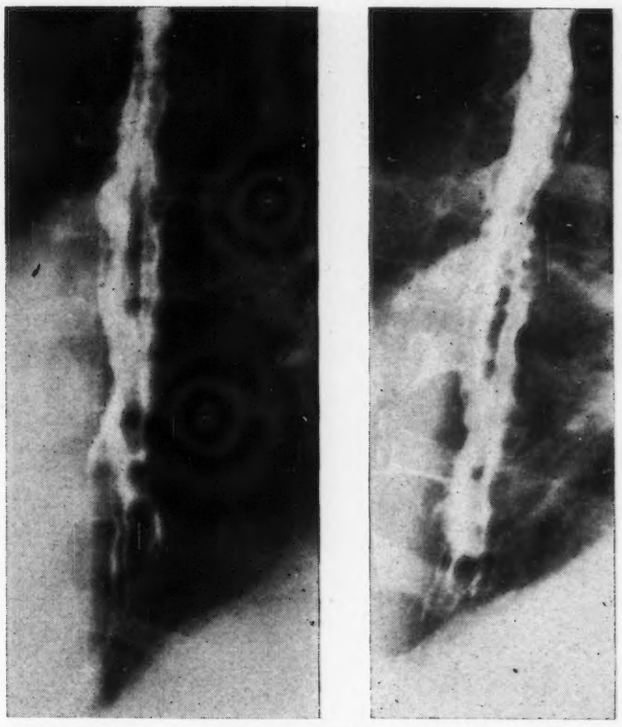


Fig. 2.—Barium swallow showing extensive œsophageal varices.

For the next four months she was able to resume her household activities, but in August 1958 the ascites rather abruptly increased in amount and she was readmitted to hospital. She was now obviously wasted. The distension of the abdomen interfered with breathing but there were no signs of heart failure. The liver extended 8 cm. below the right costal margin and the spleen 9 cm. below the left costal margin. Both were firm.

The hæmoglobin level had risen to 17.1 g. %, the red cell count to 6.9 million. The cells were slightly microcytic. The packed cell volume was 56%. The white cell count was 16,450, of which 16% were staff cells. The platelets numbered 1,120,000. The bone marrow was again hypercellular. Liver function tests were unchanged. The venous pressure measured in the right antecubital vein was 10 cm. of citrate and rose briefly to 11 cm. with pressure over the liver.

Visualization of the portal bed was accomplished by injection of 70% Diodrast into the spleen (Fig. 1). This showed remarkable hypertrophy and tortuosity of the veins in the portal area, without revealing any one vein which could be interpreted as the portal vein itself. The Diodrast remained in the liver for eight seconds, indicating intrahepatic obstruction. The films were interpreted as showing cavernous transformation of the portal vein. Injection of Diodrast into the inferior vena cava outlined an apparently normal vessel. X-ray examination of the œsophagus with barium showed large and numerous varices (Fig. 2).

Her ascites did not respond to treatment, and in October 1958 a laparotomy was undertaken with the hope of effecting an anastomosis between the portal and caval systems. Many large tortuous venous channels were encountered but none was suitable for establishing a shunt. The spleen, which weighed 740 g., was removed.

Her postoperative course was satisfactory for about one week. Her platelet count rose to 3.6 million and her white cell count to 51,800. She then developed

Canad. M. A. J.
Aug. 1, 1959, vol. 81

Fig. 3.—Collateral portal veins are shown around the fibrosed, stenotic portal vein. The left lobe of the liver exhibits a granular surface over the fibrotic tissue. An accessory spleen is present in the tail of the pancreas.

signs of mesenteric thrombosis and, in spite of vigorous therapy designed to maintain fluid and electrolyte balances, she died on the 21st postoperative day.

*Autopsy Findings*:

General examination showed the left paramedian surgical incision to be intact despite severe abdominal distension. The body appeared pale but the scleræ showed a faint icteric tinge.

Each pleural space contained about a litre of straw-coloured fluid. The lungs were crepitant and slightly œdematous. The peripheral branches of the pulmonary arteries to both lungs contained numerous small antemortem thrombi, measuring 2 to 3 mm. in diameter and 1 to 2 cm. in length. No evidence of pulmonary infarction was seen.

The heart weighed 200 g., and both it and the pericardium were normal. The coronary vessels showed minimal atheroma and were patent.

The abdominal cavity contained four litres of clear yellow ascitic fluid. The vessels of the abdominal wall were dilated and thin-walled, especially around the umbilicus and falciform ligament. Large submucosal œsophageal varices were present, but there was no evidence of ulceration or rupture in this vicinity. There was no ulceration in the stomach or duodenum. Just distal to the third part of the duodenum, the jejunum was dark blue in colour and friable in consistency, and contained jelly-like blood clot in the lumen for a distance of 26 cm. The proximal and distal aspects of this infarcted area were sharply delineated. The mesenteric veins along the border of the affected area contained firm, grey, antemortem thrombus. The larger venous branches in the mesentery appeared

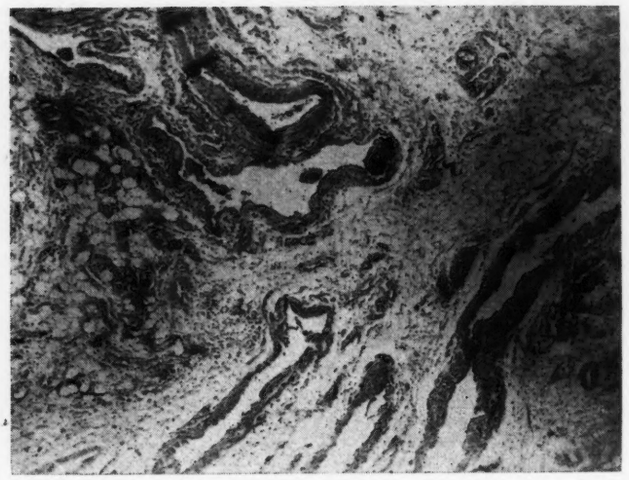


Fig. 4.—Photomicrograph of cavernous tissue showing thin-walled dilated collateral channels. × 30.

normal. Internal hæmorrhoids were the only other feature of note in the bowel. The greater omentum was adherent to the umbilicus and showed dilated veins over its entire extent.

The liver weighed 1200 g. The left lobe and peripheral edge of the right lobe presented a nodular or granular surface. The central area of the liver appeared smooth and was of normal colour. On cut section the left lobe of the liver showed a dense thick band of fibrous tissue, pale grey in colour, 3 cm. wide around the periphery. The central area of the liver was spared and appeared normal. The liver parenchyma underlying the nodular surface was composed of dense fibrous tissue. The gall-bladder was small and empty but the wall was thick and fibrotic. The bile ducts were patent. The large hepatic veins were patent.

The portal vein was represented by a fibrotic cord with isolated occlusions separated by small but patent vein lumina. The wall was thickened along the entire length. In the lesser omentum and the porta hepatis there was a network of tortuous, thin-walled veins which collapsed as dissection was attempted, making isolation impossible. These vessels surrounded the portal vein and entered the liver at the porta hepatis. Large branches were traced to the stomach and duodenum. The splenic vessels were occluded distally by a ligature and contained antemortem thrombus (see Fig. 3).

A fibrotic accessory spleen 3 cm. in diameter was found in the tail of the pancreas, which was otherwise normal. Both adrenals appeared normal, and no pathological entities were found in the kidneys or lower urinary system. The pelvic vessels contained no thrombi. The genital system was normal. The inferior vena cava was patent. Antemortem thrombi were present in the popliteal veins.

*Microscopic Examination*:

Sections through the lungs disclosed only severe congestion but no evidence of pulmonary infarction. The proximal jejunum, however, showed evidence of infarction with antemortem thrombi adherent to the intima of the mesenteric veins.

Section through the portal vein and collaterals disclosed fibrous thickening of the vessel wall with organizing thrombus in the lumen. The collaterals were thin-walled, empty and in various stages of collapse (Fig. 4).

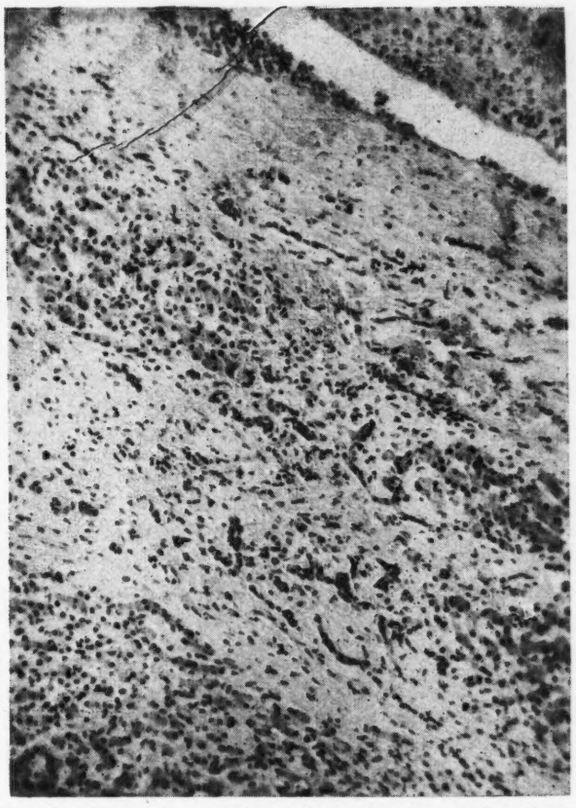


Fig. 5.—Photomicrograph of liver showing a thrombus in the hepatic vein in upper right-hand corner. Fibrosis and proliferating bile ducts are clearly shown. × 110.

The liver showed dense, fibrous bands separating groups of liver cells and proliferation of bile ductules. Some of the hepatic veins contained antemortem thrombi (Fig. 5).

## DISCUSSION

The diagnosis of polycythæmia vera in this instance rests on the following points. The presence of polycythæmia is attested by the high hæmoglobin value and red cell count and the high circulating red cell mass. No cause for secondary polycythæmia such as severe heart or lung disease was discovered. Finally the abnormal proliferation of the marrow elements and the persistent leukocytosis and thrombocytosis indicate that the hæmatopoietic mechanism was generally affected, and the disease was a manifestation of a diffuse myeloproliferative process.

Cavernous transformation of the portal vein refers to the replacement of the main portal venous channel into the liver by a mass of tortuous veins situated in the free margin of the lesser omentum and the porta hepatis.[3]

The condition is usually seen in infants and young children without intrinsic liver disease and, in such circumstances, it may represent an angiomatous abnormality.[4] Various pathogenetic mechanisms of portal vein occlusion are referred to in the literature. In general, they concern the production of extrahepatic portal bed blockage and, as a result of this, cavernous transformation of the portal vein may develop. An extension of the normal obliterative process of the umbilical vein and ductus venosus may occur at the time of birth to include the portal vein or there may be congenital hypodevelopment of the portal vein system (Cruveilhier-Baumgarten syndrome).[5] Other possibilities include congenital abnormalities or angiomata of the portal vein or inferior vena cava,[6] occlusion of the portal vein following abdominal trauma, pylephlebitis or splenectomy,[4] tumours or inflammation of the pancreas or the lymph nodes causing extra-luminal compression of the portal vein,[7] thrombocythæmia or polycythæmia vera with thrombosis of the portal vein[3] and thrombosis of the portal vein in cirrhosis.[8]

Gibson and Richards,[9] in a detailed report, present cases where no doubt exists that cavernous transformation may be the end result of acquired occlusion of the portal vein. Our case seems more readily explained by this hypothesis than by postulating a developmental anomaly or a hamartoma.

The mass of thin-walled vessels of which the cavernous tissue is composed results from compensatory dilatation of the accessory portal veins from Glisson's capsule, the lesser omentum, the gall-bladder, the bile ducts and the hepatocolic ligament. Ordinarily, these small veins empty into the portal sinus. Just as collaterals develop elsewhere in the body when the main venous channel is occluded, so the accessory portal veins develop to by-pass the obstructed area. The marked distension of the accessory portal veins is due to their anatomically exposed position. There is no firm supporting tissue in the porta hepatis to prevent the wide dilatation. Part of the cavernous tissue may be due to recanalization of thrombus in the portal vein proper. Despite the massive enlargement of the collateral channels, the efficiency of a functioning portal vein is not approached. Application of Poiseuille's law indicates that the collateral bed has to be enormous to achieve the functioning capacity of a normal portal vein.[9, 10]

The evidence of the cases of Gibson and Richards indicates that considerable time may elapse between occlusion of the portal vein and formation of the cavernous mass.[9] However, with complete occlusion of the portal vein, œsophageal varices develop in a few days to several weeks.[8] In cavernous transformation of the portal vein, there does not appear to be one massive obstruction but, rather, a series of small thrombotic episodes. These are usually not accompanied by any dramatic clinical event, if indeed they cause symptoms at all. This also is borne out by our case in which œsophageal varices were not present initially and yet, a few months later, were shown to have developed without the patient's having experienced any new symptoms.

The portal vein may be represented as a firm fibrotic functionally closed vessel, as in our case, or it may be a spongy recanalized vessel contributing to the cavernous tissue.[9]

Ascites is not a usual accompaniment of cavernous transformation of the portal vein.[9, 10] It has

Canad. M. A. J.
Aug. 1, 1959, vol. 81

been shown experimentally, by Schilling *et al.*, that simple occlusion of the portal vein in dogs is not attended by the formation of ascites. Even partial and complete occlusion of the portal vein and inferior vena cava just below the liver but above the kidneys did not produce ascites. If the inferior vena cava is partially occluded above the liver, ascites forms but does not persist. However, stasis in the hepatic veins may cause the formation of ascites which persists over a long period of time, associated closely with sodium retention, the mechanism of which is not yet clear.[11]

It has also been shown clinically that extrahepatic blockage of the portal system does not cause ascites. Ascites, when it occurs with portal hypertension, usually indicates intrahepatic fibrosis and damage.[11] Fig. 5 shows the extensive liver fibrosis and the thrombi of the hepatic vein found in the left lobe of the liver. This fits in well with the previously mentioned considerations regarding the cause of the ascites.

Patients having portal hypertension due to extrahepatic portal occlusion have a normally functioning liver and are good risks for shunt procedures. The most serious surgical risks are those cases in which the plasma albumin level is below 3 g. per 100 ml. with ascites that fails to respond to medical therapy, and which also have 3+ to 4+ cephalin flocculation tests and a depressed prothrombin activity that does not respond to vitamin K therapy. The good surgical risks have plasma albumin levels above 3 g. per 100 ml., no ascites, bromsulphalein retention below 10% in 30 minutes and a prothrombin activity within four seconds of normal (50%).

This case showed no impairment of liver function and so, except for the hazard imposed by the polycythæmia, should have been a good risk.

Portal venography has been used as a diagnostic adjunct in cases of portal vein occlusion since 1951.[12] Two methods are currently in use. In splenic portography, the dye is injected directly into splenic sinusoids and a series of films is taken at intervals of 3 to 10 seconds. Portal portography, the alternative method, requires a small laparotomy with exposure of a portal vein radicle into which the dye is injected. This is followed by a series of rapid films as in splenic portography. Splenic portography was done in our case, and the many tortuous vessels of the cavernous mass are clearly shown in Fig. 1. The œsophageal varices do not appear in this film and were demonstrated with subsequent barium swallow examination (Fig. 2).

SUMMARY

A case of polycythæmia vera in which ascites, portal hypertension and cavernous transformation of the portal vein developed is presented.

After splenectomy, the patient developed terminal mesenteric thrombosis with infarction of the bowel.

Current concepts of cavernous transformation of the portal vein are discussed.

REFERENCES

1. WHITELAW, D. M., AND THOMAS, G. C.: *Canad. M. A. J.*, 72: 128, 1955.
2. PIKE, G. M.: *New England J. Med.*, 258: 1250, 1958.
3. MACPHERSON, A. I. S., INGRAM, G. I. C. AND MACLEAN, N.: *J. Roy. Coll. Surgeons Edinburgh*, 2: 191, 1957.
4. PATTON, T. B. AND JOHNSTON, C. G.: *Am. J. M. Sc.*, 236: 239, 1958.
5. HOLLENBERG, H. G. AND BRIGGS, B. P.: *Ann. Surg.*, 141: 648, 1955.
6. JORDAN, P., JR., PATTON, T. B. AND BENSON, C. D.: *A.M.A. Arch. Surg.*, 72: 879, 1956.
7. WILCOX, A. Y., JR., BOVILL, E. G. AND OLIVETTI, R. G.: *Gastroenterology*, 21: 375, 1952.
8. Case Records of the Massachusetts General Hospital Weekly Clinics—Pathological Exercises: Case 43031, *New England J. Med.*, 256: 134, 1957.
9. GIBSON, J. B. AND RICHARDS, R. L.: *J. Path. & Bact.*, 81: 1955.
10. PARKER, R. A. AND SEAL, R. M. E.: *Ibid.*, 70: 97, 1955.
11. SCHILLING, J. A. *et al.*: *J. Clin. Invest.*, 31: 702, 1952.
12. HALLENBECK, G. A. AND BRUWER, A.: *Proc. Staff Meet. Mayo Clin.*, 29: 333, 1954.

# SHORT COMMUNICATION

## INBORN ERRORS(?) OF METABOLISM

HARRY BAKER, M.D., *Vancouver, B.C.*

MEDICAL TEACHING and medical practice are based on a miscellany of knowledge which has accumulated through the ages. There is a modicum of homogeneity to this knowledge because it relates to one factor, man, the organism within his environment. This is the only factor which lends it any cohesive quality. The actual knowledge of how man functions within his environment and how these functions relate to each other is sparse. More recently, with the influence of scientific disciplines, factual knowledge has been added more rapidly than ever before. The searchers concentrate so much on the tiny bit they seek that they tend to forget that the ultimate goal of all this searching is the biological understanding of a special organism—man, and how he functions in his environment. This ecological concept must be seen not only in space but also in time. It took man a long time to travel the various stages he did before he arrived in his present form.

Man's descent as a biological phenomenon is seldom considered seriously enough in medical teaching or medical thinking. Some medical researchers seem to ignore it. Recently with the newer knowledge of genetics and body chemistry and their various possible functions, we have begun to hear more about new diseases and their probable underlying causes. It is becoming more obvious as a result of this intensive research that we are hearing for the first time about previously unknown diseases in man. These diseases are probably due to a lack or malfunction of recently discovered enzymes. The illnesses described in this group are inherited and are present in the individual from birth or early infancy. The name applied to this group of illnesses is "inborn errors of metabolism." Garrod first used this title over 50 years ago to describe a group of rare conditions which he had studied. His clinical understanding

and acumen anticipated much that is now being said about these illnesses.

The phrase "inborn errors of metabolism" is being used very freely in the medical literature and is becoming almost a catch-phrase. Many newly described syndromes seemingly due to enzymatic disturbance are being considered under this heading. This always happens when a new idea comes to the fore. It was five decades before this one found its place. This failure to recognize earlier the value of good clinical study is probably not important. What is important is that it has not been noted that the phrase "inborn errors of metabolism" is a misleading title for the body of thought it presents.

People, in order to communicate their thoughts to each other quickly, have learned to develop words or phrases which become symbols for their ideas. When these symbols are used often enough, in time the meaning of the symbol becomes crystallized and it becomes a new whole. When a symbol thus evolved reaches this stage of its development, its original meaning becomes modified as new shades of meaning are added to it by the people who use it. These catch-phrases make for ease of communication on a superficial level. They are of value to the thinking individual because he knows their genesis and their context. When the relatively non-thinking individual uses these symbols and catch-phrases as a main channel of communication, his thinking is stultified because in his ignorance he thinks he is saying more than he is. This misuse of scientific knowledge is carried readily into non-scientific literature. Means of communication are now so readily available that "scientific" data reach many levels of thought and soon these catch-phrases are found in the lay writing, with varied meanings depending on the interpreter in question. Several ideas which have come through this cycle readily come to mind—"allergy", "psychosomatic", "stress". The phase "inborn errors of metabolism" would appear to be slated for this end. Since this is so, it would be wise to change it so that it more correctly presents what it stands for. If we think of Darwin's theory and of its biological connotation in relation to man, we cannot accept the phrase "inborn errors of metabolism".

Nature evolved many developmental patterns through the æons, in the various organisms which were produced. Man, the highest of the organisms, reflects these patterns in one way or another. He is a heterogenous conglomeration of these. Some of these patterns of development he uses well. Some are less advantageous. Man, with all his wisdom, understands very little of nature's biological laws. He has only recently, dimly, become aware of that which he is, and whence he came. Can man then label as an *error* that which he does not understand? The huge biological pattern of which he is a very small part is a mystery to him. Those factors which are disadvantageous to him, he must try to understand in their true context, not only as they affect him. While it is true that man, the individual, can only see things as they affect him and see himself in relation to others and to his environment, man, the scientist, in order to understand the biological pattern must think beyond these boundaries. It is not so long since the scientist of that day believed that the earth was the centre of the universe. Darwin more recently has shown us that man the organism is not the centre of creation. If we accept the egocentric anthropomorphic view as expressed by the phrase "inborn errors of metabolism" and neglect the point of view expressed by Darwin's theory, our biological thinking will of necessity become blurred as we blot out the larger biological pattern. If we reject the limited thinking shown by such phrases as "inborn errors of metabolism", we can hope to bring together biological data relating to man in such a way that one day man may have a better understanding of himself within his environment. This is probably why Garrod with his insight entitled his later writings *"Inborn factors in disease"*.

REFERENCES

1. GARROD, A. E.: *Lancet*, 2: 142, 1908.
2. *Idem*: Inborn factors in disease, Oxford University Press, London, 1931.

2152 West 41st Ave.,
Vancouver 13, B.C.

---

## CARCINOMA OF THE PANCREATICO-DUODENAL AREA

At the New York Presbyterian Hospital, the surgical treatment of carcinoma of the pancreas and duodenum has gone through three phases since Whipple's original operation in 1935; the pioneer period, the radical period from 1948 to 1952, and the "rational period" from 1953 to 1957. It has been found that carcinomas of the duodenum, ampulla of Vater, lower common bile duct and the non-functional islets of Langerhans are favourable lesions. The size of the lesion is not necessarily a measure of the prognosis. If the portal vein or superior mesenteric artery is involved by tumour, or lymph nodes along arteries that cannot be removed, resection is not done. Frozen sections are often examined to prove that nodes are involved or not. Biopsy of the primary pancreatic tumour is not done. No case of operable pancreatic tumour has been found in the tail of the pancreas, or in a patient with back pain severe enough to require analgesia. As the criteria for operability became more certain, the rate of operability became lower except for ampullary growths at 70%. The rest dropped from 21 to 7%. The overall operative mortality during 10 years was 16%. When total pancreatectomy was done the mortality was 30%, and when only the head of the pancreas was resected it was 11%.

The postoperative course in these cases of pancreaticoduodenectomy was satisfactory. The diabetes after total pancreatectomy was usually mild and easily controlled, and sprue could be managed with pancreatin powder.

The five-year survival rate was six out of 128 cases, none of which were carcinomas of the pancreas, but with the present criteria for operations for cure, a 50% five-year survival is being approached. Four patients developed a hæmorrhaging marginal ulcer, so that now 50% of the stomach is removed. Three of the patients surviving partial pancreatectomy developed sprue and/or diabetes long after the operation, apparently owing to stricture of the pancreatico-jejunostomy.

The medium road between unwise radical pancreaticoduodenal resection and surgical timidity is the objective sought in trying to lay down stricter criteria for operability. —M. R. Porter: *Ann. Surg.*, 148: 711, 1958.

Canad. M. A. J.
Aug. 1, 1959, vol. 81

**Special Article**

# THE THEORY OF BIOLOGIC PREDETERMINISM: ITS QUESTIONABLE USEFULNESS AND VALIDITY AS A MEDICAL TOOL

LOUIS J. NOTKIN, M.D., C.M., F.A.C.G.,
*Montreal*

THE PHRASE "biologic predeterminism" has been recurring in the medical literature and at medical meetings with increasing frequency. Ian MacDonald first employed the phrase some years ago as "a synoptic expression for a biologic balance between host and neoplasm", established before the neoplastic process becomes clinically detectable.[1-3] Evidence provided in this publication "supported an obvious corollary: the outcome of the preclinical struggle for power, between a developing neoplasm and the enigmatic defensive reactions of the host, is of greater importance than the time or type of treatment", as well as the concept that "the greater the duration of symptoms, the better the prognosis; the shorter the duration of the symptoms the poorer the prognosis."

It is intended, in this article, to examine this concept within the frame of reference of gastric lesions only.

This concept, obviously too broad, does not take cognizance of the location of the lesion. Patently a lesion interfering with the transport of gastric contents by invading a strategic area (cardia or prepyloric region) rather than by rapid infiltration or by the rapid growth of a large mass, could give rise to symptoms relatively early in the onset of the disease and could in fact contribute to make this factor a favourable one in the recovery of the patient, by drawing attention to the disease. On the other hand, a lesion in a relatively insignificant area of the stomach—the body, for instance—could achieve a considerable degree of invasion, including metastatic spread, without giving the patient more than a mild degree of difficulty, and can remain relatively asymptomatic for a protracted period of time.

Stated otherwise, it would appear that the term "biologic predeterminism" is not a yardstick which can be used in evaluating the prospects of survival of a given patient. In its broader sense the term may be considered to include all the cogent factors upon which depends the fate of the patient: the grade of malignancy of the lesion; the extent of the invasion, as well as its location, before the occurrence of symptoms; and the time at which the patient becomes aware that he is suffering from something more than a passing ailment. The time of such awareness in the life history of the disease depends largely upon the sensitiveness of the patient to discomfort, upon the presence or absence of previous gastric symptoms and upon the position of the lesion within the stomach.

The term "biologic predeterminism" would appear to be an unfortunate one because its influence is not susceptible to measurement; it connotes an almost fatalistic approach and does not appear to have any value in furthering the interests of the patient with carcinoma of the stomach. It does convey a sense of frustration, hopelessness and mysticism, and unless clarified to the point of lucidity and usefulness should be dropped.

The concept that a longer history means a more favourable prognosis in a specific cancerous lesion appears to be a very confusing, though partially true, statement of fact. It is not at all illogical to believe that patients in whom carcinoma of the stomach is diagnosed, and who have a long history, may survive longer. What appears to be illogical is the implied assumption that it is therefore not harmful, and even beneficial, to delay operation. Such an assumption can be tragically harmful if, for instance, it should be finally demonstrated that the Alice-in-Wonderland concept of *The Later The Earlier* may have a very simple explanation, namely, that the long history (in cases with favourable outcome) is merely an indication that in these patients the disease may have started as gastritis or as a benign ulcer with subsequent superimposition of malignancy. Furthermore, one must not lose sight of the fact that we do not know the length of the "silent period" in a specific patient. One factor which determines the time of onset of symptoms (and thus the duration of symptoms) is the type and location of the lesion. Contrast the adenocarcinomatous lesion of the prepyloric region with a lesion located in the body of the stomach, which may have started as a benign ulcer or as a chronic gastritis.

The concept "long history—better prognosis" may have grown out of the observation that patients with low-grade malignancy, in which instance the natural history of the lesion is a relatively long one, in truth may still be operable when they present themselves late in the history of the lesion.

Possibly a more useful concept of the life history and the significance of time in a specific instance would appear to be a multi-dimensional (time-space-intensity) concept of the lesion, where time signifies the duration of the symptoms, space denotes the area involved by the lesion, and intensity indicates the grade of malignancy. One could also include a possible fourth factor, the immunological factor suggested by Brunschwig. Obviously this multi-dimensional concept could have no prognostic value preoperatively but could be helpful postoperatively.

Dunphy,[4] in a discussion of this problem, states: "Finally, although it is evident that time alone is not the essence of successful cancer surgery, there is no reason to de-emphasize the desirability and importance of early diagnosis. Any disease should be recognized as early as possible and cancer is no exception. This should therefore be encouraged by a sensible program of public education."

An inseparable part of the problem of the early diagnosis of gastric cancer is the ulcerated carcinoma which resembles peptic ulcer and the ostensibly simple peptic ulcer which could be a peptic ulcer with superimposed malignancy.

A great deal has been written on the subject of pre-cancerous lesions. Russel Boles[5] records his belief that "Gastric ulcers, like polyps, are always potentially dangerous and can rarely be viewed with equanimity." He quotes the Gastrointestinal Cancer Committee of the National Cancer Institute of the United States Public Health Service to the effect that "although there is an epidemiologic overlap between ulcer and cancer of the stomach the principal problem lies in the field of diagnosis rather than etiology". Boles states that approximately 15% of apparently benign ulcers are found to be malignant at operation, and quotes Marshall and Welch[6] and Hayes,[7] who gave figures of 19.8 and 25 to 30% respectively. Boles does not, however, believe that radical resection of all ulcer-bearing stomachs is justifiable. "The only conscientious way I can look upon this matter is to maintain the closest vigilance on all gastric ulcers, immediately resect all those that appear malignant at the time they are first observed, and give the others the benefit of the doubt by medical management for a brief period of time. In the event of obvious lack of healing, resection would seem inescapable." He also quotes Wangensteen, who "after years of indefatigable study and effort, is enthusiastic about 'aggressive' surgery and maintains that with sufficiently early diagnosis (most cases are of two years' duration before treatment is undertaken) the five-year cure rate could be raised to approximately 50 per cent, a figure which he has attained in those patients exhibiting no lymph node involvement who had undergone gastric resection."

Predeterminism suggests too strongly the concept of predestination and carries with it a fatalistic connotation of resignation and almost of hopelessness. If the concept is intended to signify that the recalcitrance of the lesion to all forms of therapy is predetermined on the basis of its refractoriness to all therapeutic approaches, no matter how early they are instituted, then its biological relationship and union with the host is such that it is bound to remind one of *The Man Who Came to Dinner.*

There appears to be another way of interpreting the "early and late" concept. Early and late are relative terms, and while the physician has no difficulty whatever in knowing that it is too late when metastatic spread is present, he has no certain way of knowing whether the disease is very recent, recent, or has existed for some time; nor can he have the slightest intelligent notion regarding the impalpable and undeterminable role of biologic predeterminism as it applies to the patient before him. Unless this concept can be used as a differentiating standard in the decision whether or not to operate, it must remain a very interesting philosophical concept.

It has however served a very useful purpose in stimulating thinking along new lines. Is all this another way of saying that the patient with a low-grade malignancy, with a slow rate of growth and metastasis—a sort of *andante cantabile* as opposed to a relentless *crescendo*—will have a slow awakening to the idea and awareness that he is not well. He will try various home remedies, and only after realizing that the "thing" has made its home within him will he seek medical help. This concept of the long and the short history appears to make sense—the rapidly growing and metastasizing cancer, as opposed to the indolent, slowly progressing and slowly metastasizing one, elicits different responses in the respective patients and leads to different end-results. The former, while presenting himself chronologically early, is pathologically too late; the latter, presenting himself chronologically late, is, in the pathological sense, still early.

If this concept is correct, it can explain the somewhat inverted dictum "The greater the duration of the symptoms, the better the prognosis; the shorter the duration of the symptoms, the poorer the prognosis." One must stress, however, that factors previously mentioned, such as the location of the lesion (in the prepyloric area, for example), contribute towards the early recognition by the patient that all is not well. This early recognition and consequent short history serve rather to benefit the patient than otherwise.

At this point, it is rather intriguing to quote from MacDonald and his co-worker:[2] "The concept that early diagnosis of carcinoma of the stomach may improve end-results is not only fallacious but is in fact the reverse of the truth. Patients with progressively longer periods of delay from the onset of symptoms to the time of exploration enjoy increasingly better chances of resection and long-term survival. The greater the length of the history the better the prognosis." However, later in the same paragraph the authors state: "The only genuine early treatment is gastric resection for gastric ulcer which may be carcinoma." It is assumed from this statement that the authors have in mind an apparently benign gastric ulcer which, however, is the seat of an early carcinoma (presumably on the basis of a chronic ulcer rather than a primary carcinoma which had ulcerated), early enough not to be recognized as such. Is this not a degree of earliness and not of lateness?

Granting the philosophical merits of the concept of biologic predeterminism, it is the author's firm belief that, should this concept become widely known and accepted, the already deeply rooted pessimism prevalent among general practitioners regarding the value of the surgical approach in cancer of the stomach will be reinforced. This is hardly desirable.

REFERENCES

1. MACDONALD, I.: *Surg. Gynec. & Obst.*, **92**: 443, 1951.
2. MACDONALD, I. AND KOTIN, P.: *Ibid.*, **98**: 148, 1954.
3. MACDONALD, I.: *Ibid.*, **106**: 227, 1958.
4. DUNPHY, J. E.: *Ibid.*, **106**: 353, 1958.
5. BOLES, R. S.: *Gastroenterology*, **34**: 847, 1958.
6. MARSHALL, S. F. AND WELCH, M. L.: *J. A. M. A.*, **136**: 748, 1948.
7. HAYES, M. A.: *Gastroenterology*, **29**: 609, 1955.

Medical Arts Bldg.,
Montreal, Quebec.

Canad. M. A. J.
Aug. 1, 1959, vol. 81

THE CANADIAN MEDICAL ASSOCIATION
JOURNAL
LE JOURNAL DE
L'ASSOCIATION MÉDICALE CANADIENNE

*published twice a month by*
THE CANADIAN MEDICAL ASSOCIATION
*Editor:* S. S. B. GILDER, T.D., M.B., B.Sc.
*Managing Editor:* T. C. ROUTLEY, M.D., F.R.C.P.[C]
*Assistant Editor:* M. R. DUFRESNE, M.D.
*Editorial Offices:* 150 ST. GEORGE ST., TORONTO
*(Information regarding contributions and advertising will be found on the second page following the reading material.)*

## THE CHROMOSOMES OF MAN

The diploid (2n) chromosome number in somatic cells of man has been shown to be 46, rather than 48 as was formerly believed.[1-3] This revision of a a basic facet of human biology is a sequel of improved cytological methods, which include treatment of cells grown in short-term culture with colchicine and a hypotonic solution to produce more metaphase plates with less overlapping of chromosomes. Cells used for diploid counts are fibroblasts or related cell lines obtained from bone marrow, dermis, embryonal tissues or other available sources. Females have 44 autosomes and an XX-sex chromosome complex; males have 44 autosomes and an XY-sex chromosome complex. The X-chromosome pair is seventh in order of length among the 23 pairs of the complement. The Y-chromosome is much smaller, being comparable in size to the smallest of the autosomes.

Important as the foregoing advance in knowledge may be, the demonstration of heteroploidy, or abnormal chromosome numbers, as a likely etiological factor in certain developmental anomalies[4-10] is of the first importance to physicians and may forecast a new era in the study of various congenital problems. Heteroploidy has already been demonstrated in patients with Turner's syndrome, Klinefelter's syndrome, mongolism and a few cases of unclassified mental deficiency. Descriptions of other congenital abnormalities with heteroploid chromosome complements are almost certain to follow.

Heteroploidy may take the form of polyploidy, where somatic cells contain an exact multiple of the normal haploid complement of the germ cells for the species (i.e., 3n, 4n, etc.), or aneuploidy, where the count is other than an exact multiple of the haploid number. Heteroploidy is well known in plants and lower animals. It has also been observed in mammalian embryos, but has been thought of as an invariably lethal factor that is incompatible with development to birth and on to maturity. As described in detail by Beatty,[11] triploid mouse embryos have resulted from certain inter-strain matings and various forms of polyploidy have been produced experimentally. The experimental procedures include alteration of the temperature of the Fallopian tubes and addition of colchicine to semen, which suppress the first cleavage division of the zygote or the formation of polar bodies during maturation of the ovum. In the light of the following examples, it now appears that aneuploidy occurs in man spontaneously, probably because of an error in meiosis in the germ cells of one of the parents. Germ cells with a chromosome complement other than the normal haploid number are produced and participate in the production of a viable zygote. But the abnormal genotype results in an abnormal phenotype, the details depending on the particular chromosomal abnormality.

In Turner's syndrome (gonadal dysgenesis), the nuclei usually have a male or chromatin-negative pattern in contrast to the female phenotype. Ford *et al.*[4] found a chromosome number of 45 in a patient with Turner's syndrome and chromatin-negative nuclei. There were the usual 44 autosomes, but the X-chromosome was unpaired with either another X-chromosome for a female sex chromosome complex or a Y-chromosome for a male sex chromosome complex. Because of the incomplete sex chromosome complex, gonads of neither female nor male type develop, and the embryo matures along female lines in accordance with the embryological principles established by Jost.[12] The XO-sex chromosome complex in Turner's syndrome has been verified in unpublished observations by other investigators.

The chromatin pattern is female or chromatin-positive in a large proportion of phenotypical males with the Klinefelter syndrome (seminiferous tubule dysgenesis). Jacobs and Strong[5] found 47 chromosomes in a patient with the Klinefelter syndrome and chromatin-positive nuclei. The extra chromosome was contributed by an XXY-sex chromosome complex. This finding has also been confirmed by chromosome studies on similar patients. The Y-chromosome all but overcomes the female-determining factors carried by the two X-chromosomes. Although the testes are sterile, their interstitial cells are physiologically competent in the embryo and direct maturation along lines that result in a male phenotype. This demonstration of the male-determining potency of the small Y-chromosome is contrary to the prevailing view, derived from cytogenic studies on *Drosophila*, that the Y-chromosome has a passive role in the genetic mechanisms of sexual differentiation. The situation may be more complex in some cases, for Ford *et al.*[6] presented evidence for an XX/XXY mosaicism in a patient with the Klinefelter syndrome and chromatin-positive nuclei.

Many theories have been suggested in attempts to explain the cause of mongolism, but there have been few fundamental observations to incorporate in any theory, other than the well-established factor

of increasing maternal age. Recent reports of aneuploid chromosome complements in mongoloid defectives give promise that basic biological techniques and principles may at last be brought to bear on this grave medical and sociological problem. Leujeune *et al.*[7] found 47 chromosomes in three mongoloid defectives. This important finding was quickly confirmed by Jacobs *et al.*[8] in six patients. The extra chromosome was one of the smallest autosomes. So there appears to be a genetic, but not necessarily a hereditary, factor in the etiology of mongolism. Then Ford *et al.*[9] accomplished the seemingly impossible feat of consolidating the aneuploidy of mongolism and Klinefelter's syndrome in the rare instance of both conditions occurring in the same individual. There were 48 chromosomes; one extra chromosome was the small autosome of mongoloids and the other was the extra chromosome contributed by the XXY-complex of subjects with the Klinefelter syndrome!

Finally, Barr *et al.*[10] described five "non-specific" mentally defective patients whose cell nuclei contained two masses of sex chromatin. The chromosome numbers have yet to be established but the available evidence indicates that there are two XX-, or possibly two XXY-, complexes, which would introduce yet another form of aneuploidy.

The importance of these new developments can hardly be overestimated since they show that abnormal chromosome complements, in addition to mutant genes, are etiological factors in errors of human development that have a genetic basis. The probable relation of aneuploidy and mental deficiency is especially noteworthy. In addition to mongoloids with an extra autosome and the "non-specific" mental defectives with two XX-chromosome markers in their nuclei, the majority of patients with Klinefelter's syndrome and chromatin-positive nuclei (44 + XXY) show varying degrees of mental retardation. About 1% of institutionalized male mental defectives are typical, although often unrecognized, examples of the Klinefelter syndrome.

Apparently we must look to errors of chromosomal behaviour in the complex events of meiosis in germ cells as causal factors in some congenital defects. This new orientation may prove of special significance in the comparatively neglected field of basic biological research into the causes of mental deficiency.

M. L. BARR

REFERENCES

1. TJIO, J. H. AND LEVAN, A.: *Hereditas*, 42: 1, 1956.
2. FORD, C. E. AND HAMERTON, J. L.: *Nature*, 178: 1020, 1956.
3. CHU, E. H. Y. AND GILES, N. H.: *Am. J. Human Genet.*, 11: 63, 1959.
4. FORD, C. E. *et al.*: *Lancet*, 1: 711, 1959.
5. JACOBS, P. A. AND STRONG, J. A.: *Nature*, 183: 302, 1959.
6. FORD, C. E. *et al.*: *Ibid.*, 183: 1030, 1959.
7. LEUJEUNE, J., GAUTHIER, M. AND TURPIN, R.: *C. rend. Acad. Sc.*, 248: 602, 1959.
8. JACOBS, P. A. *et al.*: *Lancet*, 1: 710, 1959.
9. FORD, C. E. *et al.*: *Ibid.*, 1: 709, 1959.
10. BARR, M. L., SHAVER, E. L. AND CARR, D. H.: *Proc. Canad. Fed. Biol. Soc.*, 2: 6, 1959 (abstract).
11. BEATTY, R. A.: Parthenogenesis and Polyploidy in Mammalian Development, Cambridge University Press, London, 1957.
12. JOST, A.: *Arch. anat. micr., Paris*, 39: 577, 1950.

## *Editorial Comments*

### HYDROCHLOROTHIAZIDE—A NEW SULFONAMIDE DIURETIC

It is appropriate on the 25th anniversary of sulfonamides to pay tribute not only to their discoverer Domagk but to the chemicals themselves. In some degrees the history of sulfonamides resembles that of the old drugs such as quinine and morphine, in that some of the derivatives have entirely different properties and uses from the original. Having started out as a specific for streptococci, the sulfonamide soon developed into a general antibacterial agent and was for a while overshadowed by the emergence of antibiotics but regained its importance when the antidiabetic and, more recently, diuretic properties of its derivatives were discovered. Acetazolamide (Diamox), the carbonic anhydrase inhibitor, was the first sulfonamide to be used as an oral diuretic but was soon superseded by chlorothiazide. It was found that chlorothiazide is much less potent as a carbonic anhydrase inhibitor and depends for its main diuretic and especially chloruretic activity on some other so far unclarified mechanism. In this respect it resembles the mercurial diuretics but has in addition a property new for diuretic drugs, that of lowering elevated blood pressure. This hypotensive action has been observed both by administration of the drug by itself and by combining it with other hypotensive agents. This activity of chlorothiazide spurred on the investigation of other heterocyclic sulfonamides, and of some 125 investigated by workers in the Ciba laboratories hydrochlorothiazide (Esidrix) was found to be the most effective.

Chart *et al.*[1] report their findings in experimental animals in whom they compared the activity of hydrochlorothiazide with that of chlorothiazide. The potency of the new drug was 6.3 times higher for excretion of water, five times higher for that of sodium, four times higher for that of potassium, and 9.4 times for that of chloride. Furthermore, the diuretic and sodium excreting effect of hydrochlorothiazide was of much longer duration than that of chlorothiazide. The authors were able to demonstrate in experiments on the rat antagonistic effects of hydrochlorothiazide to vasopressin, reserpine, and syrosingopine. It also counteracted sodium and water retention produced by desoxycorticosterone acetate and aldosterone as well as the increased elimination of potassium. In adrenalectomized animals hydrochlorothiazide did not produce an increased water diuresis, and even sodium and potassium loss were only slightly increased. Under the circumstances of their particular experiments, prednisone ordinarily produces loss of sodium and potassium. With the addition of hydrochlorothiazide there was only slight potassium excretion although there was increased sodium and water diuresis. Investigations of rats in which "adrenal regeneration hypertension" and hydrocortisone hypertension was treated with hydrochlorothiazide showed that extreme hypertension was prevented in the former but no effect was obtained in the latter. Toxicity of hydrochlorothiazide must be very low indeed. Administration of large

Canad. M. A. J.
Aug. 1, 1959, vol. 81

single doses to rats and to dogs showed no untoward effect, and long-term administration of hydrochlorothiazide in very high doses caused no microscopic or histopathological changes in the tissues of four dogs.

Bartorelli, Gargano and Zanchetti[2] report from Sienna (Italy) a comparative study of the effects of hydrochlorothiazide and chlorothiazide in five normal subjects. Their conclusions are that the advantages of hydrochlorothiazide are not only quantitative but also, although to a lesser degree, qualitative. The index of sodium-excreting activity of hydrochlorothiazide was 40, that of chloride excretion 50, of potassium excretion 30 and of bicarbonate only two as compared with chlorothiazide. The urinary pH and titratable activity were not significantly modified by hydrochlorothiazide, in contrast to chlorothiazide, which is known to raise urinary pH and diminish titratable acidity.

Hejtmancik, Herrmann and Kroetz[3] of Galveston, Texas, studied 19 hospitalized and 20 ambulatory patients with œdema due to congestive heart failure who were on hydrochlorothiazide for several days to several weeks. Sixteen of the 19 in-patients had satisfactory diuresis, and of the three who failed to respond one had complicating myelofibrosis, anæmia and low serum albumin. Another had hyperthyroidism, diabetes, and renal disease with uræmia. The third patient was only partially compensated by digitalis and mercurial diuretics. Of the 20 ambulatory patients 19 had satisfactory results. It was found that 200-mg. doses were just as effective as 300-mg. doses, and that one single dose produced conspicuous diuresis in about two hours and maintained it for over 24 hours. They achieved effective diuresis with doses of 50 mg. administered twice daily but found that in a few patients levels of serum potassium below 4.0 mEq./l. appeared after one week of therapy. Only one patient in this series exhibited clinical symptoms of hypopotassæmia. Eighteen of 26 hypertensive patients showed significant reduction in blood pressure. This applied not only to patients who were in congestive heart failure but also to those who were not. The mean fall was 20 mm. Hg and occurred in the first 1-2 weeks. A relatively poor response was obtained in two patients with primary renal hypertension. Most of the patients not in congestive failure had been on syrosingopine therapy before and throughout the study, and the reduction in blood pressure in this group may have resulted from the potentiating effects of this reserpine derivative. It is expected that many more reports will appear within the next few months indicating the experience of workers with the new diuretic. At the moment, all one can say with certainty is that it is definitely more potent than chlorothiazide as a diuretic and can be very effective as a hypotensive agent. W. GROBIN

REFERENCES

1. CHART, J. J. *et al.*: *Schweiz. med. Wchnschr.*, 89: 325, 1959
2. BARTORELLI, C., GARGANO, N. AND ZANCHETTI, A.: *Ibid.*, 89: 331, 1959.
3. HEJTMANCIK, M. R., HERRMANN, G. R. AND KROETZ, F. W.: *Am. Heart J.*, 57: 490, 1959.

## PHYSICAL FITNESS

The findings of two American doctors in a recent study give some further point to the remarks on "sub-health" made in the presidential address at the recent installation of H.R.H Prince Philip, The Duke of Edinburgh. The work capacity of some 500 U.S. military and civilian air force personnel was determined by Balke and Ware of the U.S. Air Force School of Aviation Medicine, Randolph Air Force Base, Texas (*U.S. Armed Forces M.J.*, 10: 675, 1959). The test consisted of walking on a treadmill, the angle of which was raised by 1% every minute. Pulse rate, blood pressure, respiratory gas exchange during work, and pulmonary ventilation were determined before, during and after the test.

It was found that rises and falls in oxygen consumption, pulmonary ventilation, and blood pressure were not suitable as criteria for determining work capacity. The test was terminated when the subject's pulse rate attained 180 beats per minute because it had been previously found that this may serve as a critical point. Persons in the poorest physical condition attained the critical pulse rate of 180 beats per minute as early as the seventh test minute, with an average of around 15 minutes. At the other extreme, well-trained athletes were able to perform for 27 to 28 minutes before reaching this pulse rate. This preliminary study showed that physical performance of 42% of the test population was poor, that only 18% had a good or better than good working capacity, and that in the remaining 40% the performance was fair. Investigation of occupation, smoking habits, and extent of physical exercise of the subjects led Balke and Ware to conclude that the average performance capacity of people in sedentary occupations is poorest and that those who exercise intermittently have a fair capacity for work. The group which was accustomed to regular physical activity performed best and in this group work capacity was not affected to any extent by advancing age within the range of 20 to 60 years.

These findings are of particular interest to Canadian doctors in view of the challenging remarks by His Royal Highness The Prince Philip, at his installation as president of our Association. Much emphasis has been put upon the need for greater fitness by nations in ancient times as well as in more recent years. As Balke and Ware say, "History has shown that the great accomplishments of all the ancient nations were destined to perish when a peak of civilization slowly softened the physical resistance of man against the forces of nature or against the onrush of a more vital enemy. We cannot expect this pattern to change in modern times despite all technologic advancements. Unless one does not care about destiny of future generations, conscious and sustained efforts should be made to maintain the physical capacities of man at high standards." It might be added that the object of making a nation physically fit should not be allowed to degenerate, as it sometimes has in the past, into a movement towards national regimentation. It must be coupled with idealism, and the improvement of moral values.

## BEHAVIOUR PATTERN IN CARDIOVASCULAR DISEASES

At the symposium on the pathogenesis of coronary heart disease presented at the 38th annual session of the American College of Physicians in 1957, Ancel Keys *et al.* stated their hypothesis regarding the connection between hypercholesterolæmia and atherosclerosis. They considered that the main reason for the increase of cholesterol in the blood was a high-fat diet and particularly a diet in which the food oils are neutral or saturated. Population studies of Keys *et al.*,[1] Miller *et al.*,[2] and Brunner and Lobl[3] have supported the contention that in countries where the population lives on a low-fat diet the incidence of coronary artery disease is much lower than in countries where a high-fat diet is available to the population. On the other hand it is well known that emotional strain and stress are of importance in the clinical development of coronary artery disease and of myocardial infarction.

A study to evaluate the importance of emotional strain on the development of coronary artery disease is reported by Friedman and Rosenman of San Francisco.[4] They studied serum cholesterol level, frequency of arcus senilis, and incidence of coronary artery disease in three groups of men selected according to their usual overt behaviour pattern. Group A consisted of 83 men who manifested intense sustained drive for achievement, who liked to compete, and who were continuously involved in many activities requiring deadlines. The converse pattern of behaviour characterized group B, also consisting of 83 men who were free of drive, ambition, sense of urgency, or desire to compete. The third group consisted of 46 unemployed blind men living either in an institution or in their own homes and not gainfully employed. They were all suffering from financial and physical insecurity and manifested a chronic state of anxiety. All the subjects kept a dietary diary recording their intake of food and alcohol for seven days and these diaries were analyzed by competent dietitians, who found no significant differences between the three groups regarding total caloric intake or fat content of food. Serum cholesterol levels were found to be much higher in group A than in the other groups, but the clotting time was shortened only in those men of group A who had the most fully developed form of this behaviour pattern.

Clinical coronary artery disease was seven times more frequent and arcus senilis was three times more frequent in the men of group A than in those of group B or group C. Cigarette smoking, exercise, working hours, alcohol intake, and heredity were investigated but were not found to be of any pathogenic significance in the cases of clinical coronary heart disease. The authors conclude that the behaviour pattern exhibited by the men of group A was mainly responsible for their higher serum cholesterol, for shortening the clotting time, and for the marked increase in incidence of clinical coronary artery disease and arcus senilis. They refer to their previously published study of accountants whose behaviour pattern and serum cholesterol level during April, which is a deadline period, resembled those in the men of group A but in February, which was a quieter period, resembled those of men of group B.

It is of course well known that emotional stress can raise serum cholesterol levels, but so can many other factors, among which one of the most consistent is dietary fat intake. If confirmation of this study should prove the validity of the selection of patients according to overt behaviour pattern, one might assume that the atherogenic activity of a diet rich in fat or other atherogenic factors, apparently almost universal in the United States (and in Canada for that matter), can be vastly accelerated by emotional strain and stress. The validity of the criteria established by Friedman and Rosenman would have to be tested by further trials, but having granted them a validity and having accepted these findings the question arises what is to be done about them. It would also be most interesting to see the results of a similar study conducted in a country where the diet is low in fat and the incidence of coronary heart disease is much lower than in the United States. It is worth remembering that in the very young soldiers of the Korean war, the incidence of coronary artery disease among the United States troops was high and among the Koreans was very low. As cholesterol determinations in serum are notoriously inaccurate, it might be well in future to concentrate on determination of other factors such as lipoproteins. Despite their findings, Friedman and Rosenman do not deny the important role of chronic ingestion of a high-fat diet in the causation of clinical coronary artery disease. Experimental evidence of this has existed for a long time and is also supported by many epidemiological studies. If, as the authors suggest, the behaviour pattern A is becoming ubiquitous, this would be an added factor of some importance in the increasing incidence of coronary artery disease. Should we therefore concentrate our efforts on prevention of atherosclerosis by dietary restriction to the people with drive, ambition, and preoccupation with deadlines?

### REFERENCES

1. KEYS, A. *et al.*: *Ann. Int. Med.*, 48: 83, 1958.
2. MILLER, D. C. *et al.*: *Ibid.*, 49: 1178, 1958.
3. BRUNNER, D. AND LOBL, K.: *Ibid.*, 49: 733, 1958.
4. FRIEDMAN, M. AND ROSENMAN, R. H.: *J. A. M. A.*, 169: 1286, 1959.

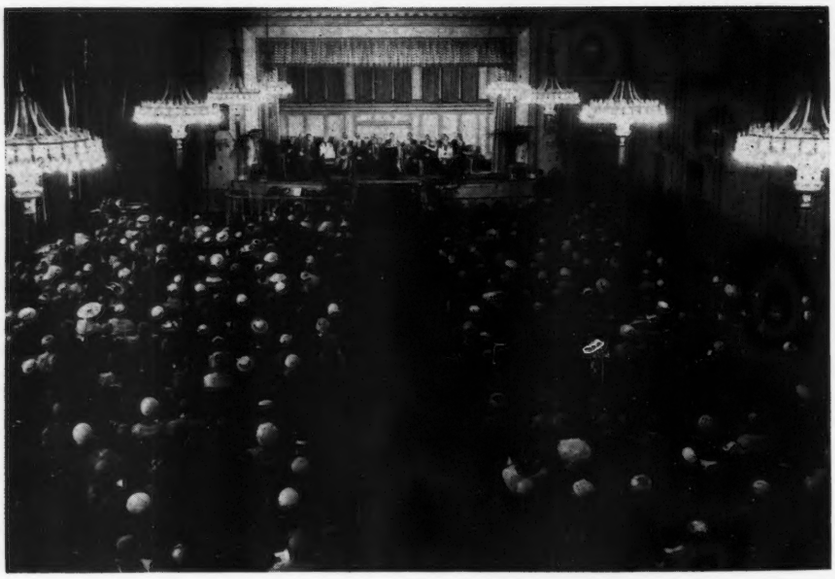
---

## AN INTELLIGENT FRIEND

"Today the golden eagle is to be found in only one small part of the globe. Tomorrow the general practitioner, another increasingly rare bird, may well be found only in Britain. In progressive countries, to the right of us and to the left of us, he is rapidly being replaced, according to political taste, by specialists or by policlinics. So far British family doctors have been reluctant to lose sight of the patient among his syndromes and systems. Their insistence on the ideals of 'continuing responsibility' and 'prevention and treatment' (to borrow the words of Dr. John Hunt, the honorary secretary of their own young and robust college) is beginning to have effect. Consultants, administrators, and laymen are slowly learning that though the patient may no longer want a father figure, or a dispenser of placebos, he still badly needs an expert and intelligent friend with first-hand knowledge of his background and medical history."—Annotation: *Lancet*, 1: 1237, 1959.

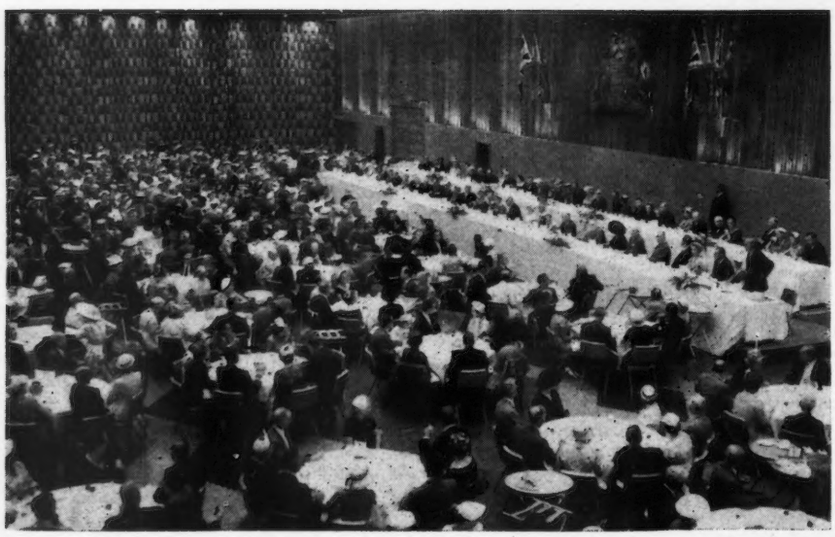
Canad. M. A. J.
Aug. 1, 1959, vol. 81

# INSTALLATION OF THE PRESIDENT OF THE C.M.A., TORONTO, JUNE 30, 1959



A general view of the 92nd Annual General Meeting, with Sir Arthur Thomson, President of the British Medical Association, delivering fraternal greetings from his Association.

Left to right: Sir Arthur Thomson, Birmingham, England, President of the B.M.A.; H.R.H. The Prince Philip, Duke of Edinburgh; Dr. Louis M. Orr, Orlando, Florida, President of the American Medical Association; Dr. Renaud Lemieux, Quebec, President-Elect of the World Medical Association; and Dr. Emile Blain, Directeur-Général, L'Association des Médecins de Langue Française du Canada.



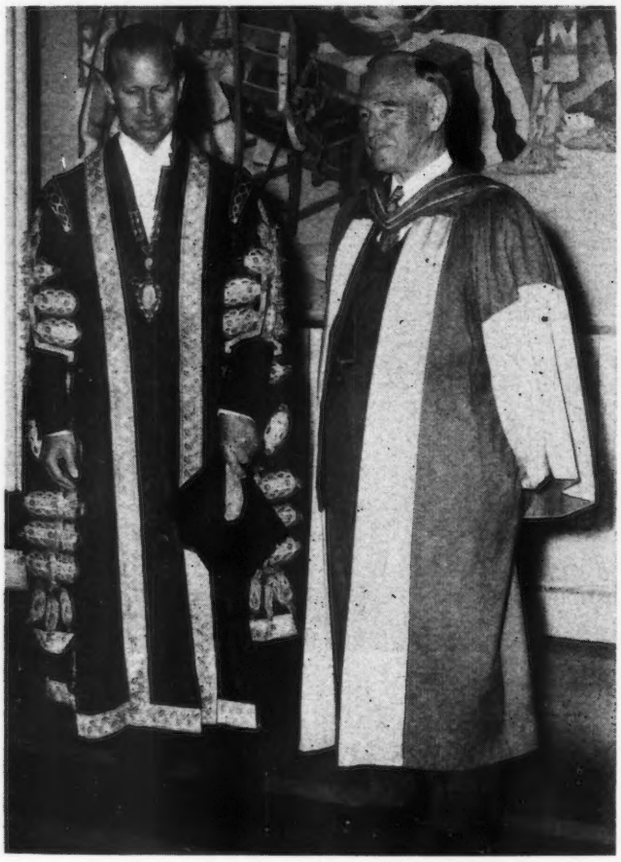
A general view of the C.M.A. luncheon in the Canadian Room of the Royal York Hotel.

In the lobby of the Royal York, the escort party meets the Prince. Left to right in the foreground: Dr. A. D. Kelly, Toronto, General Secretary of the C.M.A.; Dr. Norman H. Gosse, Halifax, Chairman of the General Council; Dr. E. Kirk Lyon, Leamington, Ontario, Deputy to His Royal Highness; H.R.H. The Prince Philip; and Dr. A. F. VanWart, Fredericton, Retiring President of the C.M.A.


Above: The President hands the chain of office to his Deputy, Dr. E. Kirk Lyon of Leamington, Ontario. The three admiring ladies are (left to right): Mrs. Norman H. Gosse, Halifax, Mrs. E. Kirk Lyon, and Mrs. A. F. VanWart of Fredericton.

Left: The new President meets the 1957-1958 President, Dr. M. A. R. Young of Lamont, Alberta. On Dr. Young's right is Mrs. G. D. W. Cameron, wife of the Deputy Minister of National Health; on his left, Mrs. M. A. R. Young and Dr. Roberta Nichols, Halifax, President of the Federation of Medical Women of Canada.

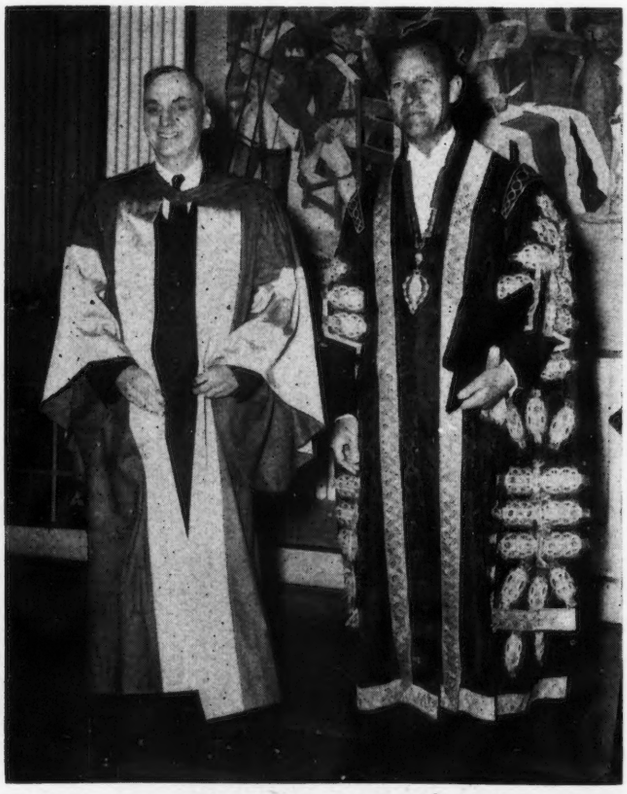
Canad. M. A. J.
Aug. 1, 1959, vol. 81



The only two Joint Presidents of the C.M.A. and the B.M.A.: H.R.H. The Prince Philip and Dr. T. C. Routley.

Prince Philip greets Dr. Margaret Gosse, wife of the Chairman of the C.M.A. General Council. Others in the reception line are (left to right): the Right Reverend F. H. Wilkinson, Bishop of Toronto, Mrs. Wilkinson, and Dr. Norman H. Gosse.

Left to right: the Hon. J. Waldo Monteith, Minister of National Health and Welfare; Dr. A. F. W. Peart, Toronto, Assistant Secretary of the C.M.A.; Dr. A. F. VanWart, Fredericton, Immediate Past President of the C.M.A.; the Hon. Herbert Bruce, Toronto; and His Royal Highness.



The Past and present Presidents of the C.M.A., Dr. A. F. VanWart and H.R.H. The Prince Philip.

*All photographs on these pages by Alex Gray, Toronto.*

# Medical News in brief

## METHODS FOR DETERMINATION OF OVULATION TIME

Two methods are reported for determining the ovulation time in women. Sevag and Colton of Philadelphia (*J. A. M. A.*, 170: 13, 1959) report a simple chemical procedure which can be performed in any laboratory or medical office. Urine samples are collected nightly between 11 p.m. and 7 a.m. beginning on the sixth or seventh day after menstrual bleeding and continuing for five to seven successive nights. They are tested by a special reagent which gives a blue colour suitable for colorimetry. The colour-yielding substance is a component of a complex containing a derivative of folic acid, but the actual chemical substances which are being tested for are not yet fully identified. The intensity of the colour increases day by day and reaches a characteristic peak after five or six days, followed by an abrupt, gentle or gradual drop in the colorimetric readings. This terminal low value represents the day of ovulation.

The test was applied to 227 cycles in which conceptions occurred by isolated coitus or by husband or donor insemination. Of the 227 conceptions 54.5% occurred during the first month of treatment. This compares very favourably with series based on basal body temperature readings and occasional vaginal smears.

Murray discusses the data reported by Sevag and Colton in the same issue of the *Journal* (p. 42) and shows how they can be used by linear correlation to estimate the day of ovulation. By applying these statistical measures he found that his data confirmed the findings of Sevag and Colton that ovulation occurs between the 10th and 15th day in nearly all cases, regardless of the length of the menstrual cycle. The range of the day of ovulation runs from 10.7 to 14.8 according to his estimates—essentially the same as in the report by Sevag and Colton. The use of his method permits determination of the probable date of ovulation if the chemical procedure is not available.

Doyle and Ewers of Boston report a method whereby Tes-Tape is applied to the cervix through a special "fertility tester" (*Ibid.*, p. 45). This consists of a narrow hollow barrel perforated at its rounded tip by an orifice through which a strip of Tes-Tape may be thrust into contact with the cervix with the plunger to which it has been affixed. After exposing it to cervical contact for three minutes, the plunger is withdrawn and the affixed Tes-Tape examined after three minutes by comparison with the three shades of green on the side of the Tes-Tape dispenser. High glucose values usually are found synchronously with ovulation and the first 2-plus reaction is utilized as a time to attempt conception. The authors suggest that the greatest usefulness of this test appears to be for patients with infertile husbands. Thus prompt conception followed isolated coitus on the 11th day when during the preceding month the glucose pattern was negative to day 9, followed by a plus reaction on day 10, a 2-plus reaction on day 11 and 12, a plus reaction on day 13 and negative reactions through the rest of the cycle. Occasionally patients show a 2-plus reaction throughout the whole cycle, and such patients may obtain better readings if hot water douching and drying of the vagina by a tampon precede the testing. In diabetics, the test is probably of limited value, and it has of course to be remembered that 25% of ova are abnormal and conception does not necessarily take place in every case. To avoid pregnancy fertile couples are advised not to have coitus until four days after the last positive glucose test.

---

## BRONCHIAL CANCER AND THE CHEMISTRY OF BRONCHIAL EPITHELIUM

In a letter to the Editor of *Nature* (183: 1743, 1959), Chayen and his colleagues from the Royal College of Surgeons, London, England, mention some histochemical studies made by them on human bronchial epithelium. They found that in basal cell hyperplasia of the bronchial epithelium, a condition common in smokers who exceed 40 cigarettes a day, the nuclei of the cells showed a very marked increase in the content or availability of lipid, probably bound phospholipid, as shown by colouring with sudan black and staining by the acid hæmatein method. Further investigation showed that this increased lipid content could be demonstrated in basal cells of otherwise normal bronchial epithelium in heavy smokers, whereas it was not present in normal epithelium from non-smokers. The cells with increased lipid content also showed selective absorption and concentration of an aqueous solution of 3,4-benzopyrene, especially in the nuclei.

This suggests to the authors the possibility that bronchial cancer may be produced in two main stages. In the first stage, damage to areas of epithelium, possibly by cigarette smoking, might alter them in such a way as to increase their affinity for lipid-soluble substances, leading to preferential absorption of carcinogens in the second stage.

---

## WARTS IN SCHOOL-CHILDREN

Among 4240 Dutch school-children examined by van der Werf (*Nederl. tijdschr. geneesk.*, 103: 1204, 1959) 308 (7.2%) were found to have warts. Curiously enough, none of these patients had plantar warts; most of the warts were found on the arms and hands. The two sexes were equally represented, and the incidence of the affection increased with age from 4.5% in the earliest grade to 12% in the 8th year of school. The incidence of warts varied very greatly from school to school, and it was also noted that in half the affected children other members of the family also suffered from warts. It would seem that school and family contacts are of significance in spreading the condition.

The most significant observation was that in 89 out of 136 cases (65%) followed up for about two years, the warts had disappeared without any treatment. This is a fact which must always be taken into account in assessing the results of so-called cures.

*(Continued on advertising page 36)*

Canad. M. A. J.
Aug. 1, 1959, vol. 81

# REVIEW ARTICLE

## CONDUITE A TENIR DEVANT UN HYPERTENDU JEUNE*

P. MILLIEZ et D. FRITEL, *Paris, France*

LA DÉCOUVERTE, chez un sujet jeune, d'une hypertension artérielle permanente et générale impose: l'appréciation de son retentissement vasculaire; la recherche d'une étiologie précise; une attitude thérapeutique.

### I. LE RETENTISSEMENT VASCULAIRE

La palpation des artères périphériques juge de l'importance de la sclérose et d'éventuelles thromboses. L'examen du fond d'œil, associé à la prise de la pression de l'artère rétinienne, renseigne sur l'état des artérioles (sinuosité des artères, irrégularités de calibre, écrasement des veines par les artérioles) et sur la perméabilité des vaisseaux (thromboses, hémorragies, exsudats, œdème). L'état du cœur doit être bien précisé. Après l'interrogatoire soigneux, une bonne auscultation, l'examen radiologique apprécie la déviation, l'augmentation de calibre de l'aorte et le volume du ventricule gauche. L'électrocardiogramme peut se montrer normal ou présenter des signes d'hypertrophie ventriculaire gauche, des signes coronariens.

L'altération du fonctionnement rénal permet de juger de l'atteinte artériolo-capillaire de cet organe particulièrement vascularisé. L'examen complet des urines (recherche d'une albuminurie, culot urinaire avec culture, numération des hématies et leucocytes éliminés par minute) et les épreuves fonctionnelles classiques associées si besoin à la mesure des clearances glomérulaire et tubulaire sont nécessaires.

Enfin certains tests très simples étudient la régulation tensionnelle: test d'effort et test au froid.

### II. LES RECHERCHES ÉTIOLOGIQUES

L'ensemble de ces examens permet d'apprécier le degré de gravité et l'évolutivité de l'hypertension artérielle, mais il ne faut pas oublier que l'hypertension n'est qu'un symptôme: l'examen d'un hypertendu jeune doit donc de toute nécessité comporter la recherche, d'autant plus acharnée que le sujet est plus jeune, d'une étiologie, essentiellement rénale ou surrénale; l'hypertension artérielle essentielle doit voir son cadre se rétrécir chaque jour.

#### *Les hypertensions d'origine rénale*

Le plus souvent, l'hypertension artérielle est en rapport avec des lésions rénales bilatérales, qui sont au-dessus de toute ressource thérapeutique, qu'il s'agisse de glomérulo-néphrite chronique, de néphrite interstitielle ascendante, de néphro-angiosclérose ou d'anomalies congénitales (polykystose et aplasie rénale bilatérale, malformation des voies excrétrices). Bien que plus rares, les hypertensions par anomalie rénale unilatérale doivent être recherchées avec soin en raison des possibilités de guérison radicale. Seules les explorations radiologiques permettent le diagnostic (Fig. 1).

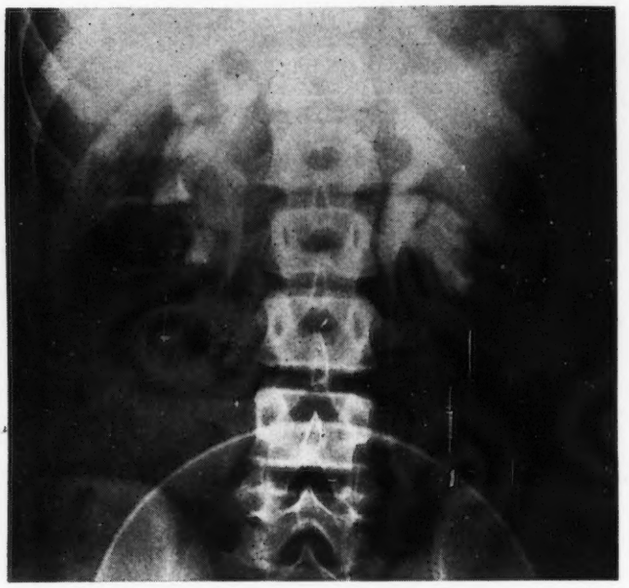


**Fig. 1.—La pyélographie d'élimination montre une atrophie rénale droite liée à un reflux urétéral. Cette fillette de 11 ans, qui présentait une hypertension maligne, obtint une guérison après néphrectomie. (Hôpital Broussais-La Charité)**

L'urographie intraveineuse constitue une investigation capitale; l'examen couché sera toujours complété par la prise d'un cliché en position verticale et par une cystographie pré puis post-mictionnelle. Dans plus de la moitié des cas, l'anomalie rénale unilatérale consiste en une pyélonéphrite atrophique, plus rarement il s'agit d'une tuberculose rénale, d'une hydronéphrose ou d'un rein lithiasique. Une maladie du col avec distension et reflux peut être à l'origine d'une néphrite ascendante sans qu'il y ait nécessairement de résidu vésical: la radiocinématographie du bas appareil urinaire est alors particulièrement instructive.

La $\gamma$-radiographie, nouvelle venue en pathologie rénale, apporte des données fort intéressantes et simples sur le fonctionnement séparé des deux reins.

La pyélographie rétrograde n'est indiquée que lorsque l'un des reins n'apparaît pas à l'urographie. On profitera parfois de cet examen pour effectuer en même temps une séparation des urines en vue de l'étude fonctionnelle séparée de chaque rein.

Le rétropneumopéritoine, qui doit comporter, en dehors des clichés standard, des coupes tomographiques indispensables pour un diagnostic précis, met parfois en évidence une anomalie rénale ou une atrophie unilatérale; cette méthode peut même faire découvrir un rein aplasique alors que les autres investigations tendent à conclure à une agénésie rénale.

L'artériographie rénale précise des lésions vasculaires, génératrices d'hypertension artérielle, alors

*Travail présenté à Chicoutimi le 7 mai 1959 lors de la 21e réunion annuelle de la division du Québec de l'Association Médicale Canadienne.

même que l'urographie donne des résultats normaux ou ne révèle que des anomalies très minimes. L'artériographie, pratiquée de préférence par voie fémorale (car cette technique simple permet l'injection de la plus petite quantité de produit de contraste), se décompose en deux temps: temps artériel, étudiant l'artère rénale et ses branches, temps néphrographique, appréciant le volume du rein et l'importance de la sécrétion rénale, et parfois temps urographique. L'artériographie rénale peut montrer une thrombose, un rétrécissement localisé ou étendu d'une artère rénale, un anévrysme artériel ou artérioveineux, la compression d'une artère par une tumeur.

Complément de l'artériographie, la phlébographie rénale est difficile à réaliser en raison de la vitesse et de la pression élevée du flux veineux rénal qui empêchent habituellement l'opacification à contre-courant de la veine rénale.

Lorsque les explorations radiologiques ont permis de rattacher l'hypertension artérielle à une lésion rénale unilatérale (19 fois sur nos 531 hypertendus), la sanction thérapeutique doit être chirurgicale car il s'agit de sujets jeunes, dont l'hypertension se montre d'une haute gravité: la seule chance de guérison est la néphrectomie dont les résultats sont parmi les plus favorables en matière d'hypertension (7 fois sur 19).

*Les hypertensions d'origine surrénale*

Une origine surrénale, médullaire ou corticale, doit toujours être recherchée systématiquement, d'autant plus que là encore le traitement chirurgical peut amener la guérison totale de l'hypertension artérielle.

En premier lieu s'impose la recherche d'un médullosurrénalome. Certes, un phéochromocytome peut se traduire cliniquement par l'apparition d'accès hypertensifs paroxystiques chez un sujet normotendu ou hypertendu permanent, mais il se manifeste au moins aussi souvent également sous l'aspect d'une hypertension permanente banale (2 fois sur nos 531 hypertendus). Ceci démontre l'intérêt de la pratique systématique du test à la régitine: l'injection intraveineuse de 5 mg. de régitine provoque, en cas de phéochromocytome, une chute tensionnelle immédiate, importante et prolongée. La confirmation du diagnostic repose sur deux examens: le dosage des catécholamines urinaires, qui donne des chiffres quatre à dix fois supérieurs à ceux des sujets normaux, et le rétropneumopéritoine, qui montre une opacité arrondie, de siège surrénalien ou para-surrénalien. Le traitement est chirurgical.

L'hypertension artérielle d'origine cortico-surrénale le plus souvent rencontrée est celle du syndrome de Cushing. Ce diagnostic, soulevé dès l'inspection du malade, doit être confirmé par le dosage des 17-hydroxycorticostéroïdes, et des 17-cétostéroïdes, qui met en évidence le trouble biologique caractéristique de ce syndrome, l'augmentation des glucocorticoïdes associée ou non à l'augmentation des 17-cétostéroïdes. En outre le diagnostic étiologique de ce syndrome de Cushing (cancer, adénome ou hypertrophie) peut être affirmé dans un grand nombre de cas par les dosages hormonaux après deux épreuves dynamiques: l'épreuve de stimulation par l'A.C.T.H. et l'épreuve de freination hypophysaire par la delta-cortisone. Le rétropneumopéritoine montre, en cas de tumeur cortico-surrénale, une opacité surrénale anormale dans sa forme et son volume. Lorsque le diagnostic étiologique reste litigieux, une exploration chirurgicale s'impose: on fera une surrénalectomie unilatérale en cas de tumeur, une surrénalectomie bilatérale subtotale ou même totale en cas d'hyperplasie.

Enfin, dernier type assez rare d'hypertension d'origine surrénale, l'hypertension artérielle de l'hyperaldostéronisme primaire ou syndrome de Conn, lié à un adénome ou à un carcinome corticosurrénal sécréteur d'aldostérone. On doit y penser lorsqu'un hypertendu présente une polyurie, une polydipsie, une asthénie musculaire chronique associée parfois à des paralysies périodiques et à des crises de tétanie. Le syndrome biologique est très particulier: dans le sang, une hypokaliémie, une hypernatrémie et une augmentation de la réserve alcaline; dans les urines, une hyperkaliurie, un pH alcalin et une densité basse. La confirmation du diagnostic est apportée par le dosage de l'aldostérone urinaire et le rétropneumopéritoine.

*L'hypertension permanente essentielle*

Malgré les progrès des investigations radiologiques et hormonales, les hypertensions artérielles d'origine rénale ou surrénale curables chirurgicalement ne sont pas encore les plus fréquentes. Souvent, aucune étiologie curable n'est découverte (235 fois sur 531): dans ces cas, une seule donnée est fréquemment retrouvée chez les sujets jeunes: une hérédité hypertensive grave.

L'hypertension essentielle ne relève que d'un traitement symptomatique, qui peut être médical ou chirurgical.

Le traitement médical doit toujours être tenté en premier lieu; il s'appuie sur trois grands éléments: le repos, les médications hypotensives, la diététique.

Le repos, physique et moral, est un élément essentiel du traitement; il peut parfois entraîner la normalisation des chiffres tensionnels. Les médications hypotensives sont variées, mais les principales sont les hydrazinophtalazines et surtout les alcaloïdes du Rauwolfia qui, outre leur action hypotensive, possèdent une action neuro-sédative très nette. La chlorothiazide et ses dérivés semblent un utile appoint. Il est également toujours indispensable de faire un essai bien conduit du régime désodé, qui ne doit pas être carencé, mais varié et relevé par divers condiments.

Lorsque la gravité de l'hypertension paraît mettre en jeu à brève échéance la vie du sujet de moins de

Canad. M. A. J.
Aug. 1, 1959, vol. 81

50 ans, le traitement chirurgical (90 fois sur nos 531 malades) est le seul recours, en sachant que l'insuffisance rénale constitue cependant une contre-indication absolue. A l'opération de Smithwick, il paraît souhaitable d'adjoindre une intervention surrénalienne bilatérale, subtotale. Ces interventions comportent une mortalité opératoire d'environ 5% et n'entraînent de guérison apparemment complète que dans 25% des cas; dans les 75 autres cas sur 100, malgré la persistance d'une tension artérielle élevée, les troubles fonctionnels disparaissent, les lésions du fond d'œil sont améliorées, les médications hypotensives voient leur activité renforcée et le plus souvent le sujet peut reprendre une activité professionnelle normale.

SUMMARY

The discovery of a continuing arterial hypertension in a young person means that the physician must do three things: (1) evaluate its effects on the vascular system; (2) look for the exact cause of the hypertension; (3) decide on a plan of treatment.

Assessment of vascular effects depends on study of the peripheral arteries, examination of the ocular fundus, examination of the heart physically, radiologically and by electrocardiogram, and study of renal function, and of responses of blood pressure to effort and cold.

It must be remembered that hypertension is only a symptom and that the younger the subject, the more necessary it is to find the exact cause. Hypertension is very frequently related to bilateral renal lesions, although the presence of a unilateral renal lesion should be looked for also. Intravenous urography is very important, not omitting a radiograph with the subject standing up and a cystogram before and after micturition. Radiocinematography of the lower urinary tract may be particularly useful, as may gamma radiography. Retrograde pyelography is indicated only if one of the kidneys is not visualized. A retropneumoperitoneum is also helpful, particularly in discovering an aplasia of the kidney. Renal arteriography may demonstrate vascular lesions otherwise undiscovered—thrombosis, stricture of the renal artery, aneurysm or compression of an artery by a tumour. Renal phlebography is much more difficult. In 19 cases out of 531 of hypertension in young persons, radiological examination revealed a unilateral lesion of the kidney; in such cases, the only chance of cure is by nephrectomy, which gives favourable results.

A lesion of the adrenal medulla or cortex ought always to be sought for, particularly as its surgical treatment may lead to a complete cure. Phæochromocytoma sometimes causes a continued hypertension, and in such cases the Regitine test, the quantitative measurement of urinary excretion of catecholamines, and the demonstration of a tumour by retropneumoperitoneum are helpful. The commonest lesion of the adrenal cortex is Cushing's syndrome, the diagnosis being confirmed by estimation of steroids in the urine, particularly after stimulation with ACTH or after pituitary inhibition by delta-cortisone. In doubtful cases, surgical exploration is necessary. Finally, a primary hyperaldosteronism may be the cause of the hypertension, associated with an adenoma or carcinoma of the cortex. The biological syndrome in these cases is very characteristic, with low potassium, high sodium and alkaline reserve in the blood and high potassium in the urine.

When radiological and endocrine investigations fail to reveal a curable condition, we are left with an essential hypertension of which symptomatic treatment is the only possibility. This is based on rest, hypotensive drugs and diet.

# GENERAL PRACTICE

## THERAPEUTIC TRIALS OF NEW PHARMACEUTICAL PRODUCTS

SEVERAL clinical research projects are now under way in various parts of Canada under the ægis of the Central Committee on Clinical Research of the College of General Practice. These studies, and those which will follow, will help to solve many riddles in medicine which have long gone unsolved because only the general practitioner holds the key. Information of vast importance in the natural history, the epidemiology, the social and economic implications, the clinical aspects, and the pathological processes of many diseases can be provided only by the general practitioner. This fact applies equally in the field of therapeutics.

Recognizing this, the medical directors of the Canadian Pharmaceutical Manufacturers Association decided that they would like to make use of the services of interested general practitioners in trying out new compounds in everyday routine practice. This has been done already on a limited scale and the results obtained have indicated that important differences in opinion regarding drugs are registered by general practitioners as opposed to those men in the larger research centres.

Having thus decided, official representation was made to the Committee on Research of the College, and this committee also approved of the plan and decided to incorporate it into its activities.

The normal course of events before the actual marketing of a new drug is as follows. When the basic chemical work is completed and a new compound obtained which holds promise of therapeutic merit, the drug is then subjected to exhaustive pharmacological and toxicological studies in appropriate animals. If these studies are satisfactory, the next step taken is the study of the toxicology and pharmacology of the drug in humans. Provided this investigation is acceptable, clinical trials are set up in various research centres and the therapeutic worth of the drug is established. If the preparation is considered useful by the clinical investigators, all the accumulated data—chemical and animal and human toxicological and pharmacological, along with the results of clinical trials—are submitted to the Director, Food and Drug Directorate, Department of National Health and Welfare, Ottawa. When he has officially approved the drug, it can be manufactured and marketed.

After official approval and actual marketing, there is an inevitable time-lag. It is during this period that the medical directors of the Canadian Pharmaceutical Manufacturers Association would like to see a new therapeutic agent used by a few selected practitioners, for they are convinced that this would result in valuable, practical information. It must be emphasized that if this is done the physicians doing the work will be provided with supplies of a drug which has been thoroughly investigated, has been approved by federal authorities, and is actually to appear on the market

in a short time. Therefore, there need be no reservations as to its use on patients.

A list of general practitioners who would be interested in this type of clinical investigation is required. Such a list, once completed, will be made available to the medical directors of the various pharmaceutical firms who will use the list to select physicians to try out new products. All members of the College who would be interested in such clinical therapeutic studies are invited to submit their names to the Secretary of the Central Committee on Clinical Research.

---

## FIELD STUDY OF VIRUS DISEASES IN GENERAL PRACTICE

AS RECENTLY STATED at the Scientific Assembly of the College of General Practice, in Toronto, there is increasing evidence that many illnesses commonly encountered in general practice are manifestations of a virus infection. It is the purpose of this notice to seek the collaboration of general physicians in the vicinity of Toronto in the investigation of illnesses of presumed virus etiology.

From July 6, 1959, Dr. John MacAulay, who has had specialized training in internal medicine and cardiology recently at Sunnybrook Hospital, will be available to conduct field and clinical investigations in collaboration with Dr. A. J. Rhodes and his colleagues at the School of Hygiene. Dr. MacAulay may be reached at the School of Hygiene, University of Toronto (phone WA. 3-6611, locals 523 or 513) during working hours, or at home (BE. 3-1803) at other times.

Practitioners are invited to get in touch with Dr. MacAulay in the investigation of the following clinical entities:

1. *Epidemics of febrile illnesses* with unusual rashes, signs of aseptic meningitis, heart involvement, or myalgia. Some of these illnesses may be tentatively diagnosed as "German measles" or "rubelliform rashes". Previous experience suggests that the newly discovered Echo viruses may be responsible for many of these infections. Particular interest attaches to the study of acute cases of German measles, for nobody has yet succeeded in isolating the causal agent of this disease.

2. *Cases of acute myocarditis, pericarditis, or heart failure of uncertain etiology.* There is increasing evidence that viruses are the causal agents in many cases of "idiopathic" myocarditis and pericarditis. To date, most of the evidence concerns Coxsackie B viruses, some strains of which have actually been isolated from the myocardium or pericardium.

Practitioners are invited to seek our collaboration in the study of the above-listed syndromes. Dr. MacAulay will visit the patient, under your supervision, take the necessary samples of blood, throat washings and fæces, and send you the results of the laboratory tests in due course.—A. J. Rhodes, M.D., F.R.C.P.(Edin.), F.R.S.C., Director, School of Hygiene, University of Toronto.

# WORLD MEDICAL ASSOCIATION

## ASSEMBLY OF THE WORLD MEDICAL ASSOCIATION

The great attraction of the joint meeting of the Canadian and British Medical Associations this year in Edinburgh should not make Canadian physicians lose sight of the fact that there is going to be an international gathering in Montreal early in September at which local observers will be welcome and in which a number of the events will be of very general interest.

The Thirteenth General Assembly of the World Medical Association is going to be held at the Queen Elizabeth Hotel, Montreal, from Monday, September 7, to Friday, September 12, and will attract delegates from a great number of national medical associations. On Sunday, September 6, the Council of the W.M.A. will be meeting in the hotel and on Monday, September 7, delegates will be registering, and some will be visiting the Montreal General Hospital and the Notre-Dame Hospital. In the afternoon the medical editors will get together with representatives of such media as television, films, radio and tape-recordings to discuss their relative values and places in medical communications.

After this "warming-up" period, the Assembly will go into its opening plenary session on Tuesday morning, September 8. It will have the honour of being addressed by the Minister of National Health and Welfare, the Honourable Waldo Monteith, and representatives of the province of Quebec and the city of Montreal. At this ceremonial session, our own Dr. Renaud Lemieux will be installed as President for 1959-1960, and the morning will end with the official opening of the technical and commercial exhibit. On Tuesday afternoon the plenary session will continue with a keynote address by Dr. Norman H. Gosse of Halifax, after which Council will report to the Assembly. The session will end with a number of reports from regional secretaries, the executive editor, and editorial board, etc. At 5:30 the delegates will be taken to a Civic Reception by the City of Montreal at The Chalet.

Wednesday morning will see a number of committee reports given to the plenary session. These will concern such important subjects as medical education, medical ethics, and international liaison. In particular, the relationships between organized medicine and such bodies as W.H.O. and the I.L.O. will come in for discussion. In the afternoon, the delegates will listen to Professor Hans Selye on "Stress and Cardiac Infarcts" and Professor Ronald V. Christie on "Chronic Bronchitis and Emphysema", after which they will be taken on a tour of the Pharmacological Research Laboratories of Ayerst, McKenna and Harrison Limited.

On Thursday morning, there will be more committee reports, including that of the extremely important planning and finance committee of the W.M.A. The afternoon will be devoted to a panel discussion on "The North American Approach to Health Insurance", in which Dr. J. A. McMillan of Prince Edward Island will be the moderator, assisted by panellists from Canada and the U.S.A. On Thursday evening the delegates will be the hosts of the Canadian Medical Association at a cocktail party and the Annual Dinner. The highlight of Friday, in which the plenary session will go on all day, will be discussion of the committee

Canad. M. A. J.
Aug. 1, 1959, vol. 81

report on socio-medical affairs. The exhausted delegates will be taken on Saturday for a trip to the St. Lawrence Seaway.

Visitors are reminded that there will be a technical and scientific exhibition chosen with care and manned by multilingual personnel. A special program for the ladies has also been arranged.

---

# MEDICAL MEETINGS

## MEDICAL LIBRARY ASSOCIATION

For the first time in the 58 years of existence of the Medical Library Association, its annual convention was held in the city of Toronto, on June 15 to 19, 1959. Registration at the King Edward-Sheraton Hotel for this event was very satisfactory, for approximately 400 medical librarians from all over North America joined in the packed program. On the Saturday preceding the convention, a large number of librarians attended short refresher courses, which included courses on medical nomenclature by Professor J. W. A. Duckworth, Professor of Anatomy, University of Toronto, and medical writing by the Editor of this Journal.

The main theme of the convention was "Canada's Contribution to Medical Progress" and contributors to this symposium included Dr. W. R. Feasby, who outlined the history of the discovery of insulin; Dr. J. K. W. Ferguson, who delivered a general paper on Canadian milestones in medical research; Dr. R. Ian Macdonald, who described Canadian milestones in clinical medicine; and Dr. Stuart D. Gordon, who spoke on contributions of surgeons to Upper Canada. The final medical contribution came from Dr. A. L. Chute, who described Canadian pædiatric contributions to medical progress. Other papers dealt with the National Science Foundation's scientific information programs, the libraries of medical and dental faculties and schools in Canada (given by Miss Doreen E. Fraser, University of British Columbia Bio-Medical Library), and pharmacy and public health in Canada (given by Dean F. N. Hughes of the Faculty of Pharmacy, Toronto).

On Tuesday morning, the University of Toronto library staff played host and in the afternoon the Academy of Medicine library staff took over. The afternoon's proceedings included a panel on "The Medical Editor, Author and Librarian as a Team" with the Editor of this Journal as moderator and Drs. R. M. Janes, R. A. Gordon, Elizabeth Chant Robertson and W. B. Spaulding and Mr. W. K. Beatty (Medical Librarian, University of Missouri) as panelists. The comments of visiting librarians from the States suggested that the local committee, with Miss Marian A. Patterson as Chairman, had produced an outstanding program. Highlights of the social program included a reception in the Vice-Regal Suite at the Parliament Buildings when His Honour Justice J. Keiller Mackay, Lieutenant-Governor of the Province of Ontario, graciously received the visiting librarians, and the Annual Banquet of the Association at which Dr. William Boyd was the guest speaker.

# LETTERS TO THE EDITOR

## APATHETIC HYPERTHYROIDISM

*To the Editor*:

In the May 15 issue of the Journal (*Canad. M. A. J.*, 80: 805, 1959) Drs. D. L. Wilansky, N. Kalant and J. Wolfson report on thyroid function in "apathetic hyperthyroidism". In this connection, they emphasize the value of scanning in the diagnosis of hyperthyroidism in patients with borderline $I^{131}$ uptake values. The wording suggests that hyperthyroidism is the most likely diagnosis in patients with borderline $I^{131}$ uptakes in whom localized areas of $I^{131}$ uptake are found.

In this laboratory, this phenomenon has been less commonly associated with any type of hyperthyroidism. Of 69 cases in which a localized area of radioactive iodine uptake was found in the thyroid gland, with low uptake in the surrounding thyroid tissue, only 14 cases were hyperthyroid. Of these, six were cases of classical hyperthyroidism with hyperkinetic activity, rapid speech, fine tremor, and pronounced tachycardia. True exophthalmos was present in one case. (Their 10-minute uptakes ranged from 3.7% to 20%,[1] their 24-hour uptakes from 51% to 72%, and P.B.I. from 8.3 μg. % to 14 μg. %.)

Eight of the 14 cases could be classified as "masked" hyperthyroidism, though only three cases showed "apathy". Their 10-minute uptakes varied from 1.7% to 13%, their 24-hour uptakes from 32% to 85% and their P.B.I.'s from 7.1 μg. % to 12.8 μg. %. Their final diagnosis was made only after careful clinical evaluation and response to treatment.

There can be no quarrel with Dr. Wilansky's suggestion that hyperthyroidism associated with a "hot nodule" is a different entity from classical hyperthyroidism associated with either diffuse goitre or nodular goitre, but the suggestion that this type of hyperthyroidism is the only one responsible for "masked" or "latent" or "apathetic" hyperthyroidism is open to question. Further, such patients may manifest "*classical hyperthyroidism*".

Scanning patients with hyperthyroidism would seem of little value in assessing the degree of "toxicity" as compared with clinical evaluation, but may give useful information regarding pathogenesis.

H. P. HIGGINS, M.D., F.R.C.P.[C],
Director, Radioactive Isotope Laboratory,
St. Michael's Hospital,
Toronto, Ontario,
July 3, 1959.

REFERENCE

1. HIGGINS, H. P.: *J. Clin. Endocrinol.*, 19: 557, 1959.

---

## PREVENTION OF SIPHON ACTIVITY IN THE APPARATUS DURING EXCHANGE TRANSFUSION

*To the Editor*:

During the course of an exchange transfusion in infants, when the Kaessler exchange transfusion set is used, it has been observed that a considerable amount of blood is wasted if the flasks or bottles containing the

blood are not kept at proper levels. This fact is apparently known to many pædiatricians who use this apparatus frequently. However, persons not used to this apparatus are liable to keep the reservoirs of the blood at incorrect levels resulting in considerable wastage of blood.

At the beginning of the exchange transfusion the level of the blood in the almost-full "donor-flask" is much higher than that in the almost-empty "discarded-blood flask". This difference in the levels of blood in the flasks, connected to each other through the two-way glass valve and the tubing filled with the column of blood, produces a siphon activity, by virtue of which the unused blood slowly flows and collects in the "discarded-blood flask", often unnoticed by the operators.

In a small experiment, carried out in the Research Laboratory, Department of Pædiatrics, it was demonstrated that when both the flasks (500 c.c. Ehrlenmeyer flask) were kept at the same level, and the "donor-flask" was filled with 500 c.c. of human blood, the initial difference between the levels of the blood in each flask was about 4½ inches (11.25 cm.). For the first 50 c.c. and for each subsequent 50 c.c. of the blood, in presence of the wire-gauze filter, it took approximately 2, 5, 10, 40, and more than 80 minutes, respectively, to flow from the "donor-flask" to the "discarded-blood flask", because of the siphon activity. These observations illustrate the approximate rate of wastage of the blood if both flasks are kept at the same level. This rate increased in the absence of the filter.

The siphon activity thus produced is very easily and simply preventable. The only point to be made sure of is that the level of the blood in the "donor-flask" must not be higher than that in the "discarded-blood flask", at any stage during the exchange. This is made possible by keeping the "discarded-blood flask" at a higher level (for example on a block of wood or an inverted bowl) than the "donor-flask". If it is desired to use the bottle instead of the "donor-flask", then this must be hung at a lower level than that of the "discarded-blood flask".

ZAFAR H. ZAIDI, M.B., B.S.,
Chief Resident in Pædiatrics,
Ottawa General Hospital, and Department of Pædiatrics, University of Ottawa,
Ottawa, Ont.
June 29, 1959.

---

# THE LONDON LETTER

*(From our own correspondent)*

### EXPERIMENTAL SURGICAL UNIT

Once again the Postgraduate Medical School of London is in the news. This time it is the opening of a new Experimental Surgical Unit. This has been made possible by a grant of £80,000 from the Wellcome Trust and £55,000 from the University of London. Whilst the new laboratories, which were officially opened by Sir James Paterson Ross, the President of the Royal College of Surgeons of England, are intended primarily for the department of surgery of the Postgraduate Medical School, their facilities will be available for other departments of surgery in the British Postgraduate Medical Federation. The opening of this new Unit will go far towards filling a serious gap in medical research in this country. During recent years it has become increasingly evident that the facilities for experimental surgery were wholly inadequate, and young surgeons have had difficulty in finding laboratories in which they could carry out their research activities. The Royal College of Surgeons has done what it could, but it has been clear for many years that surgical progress could not be maintained unless further laboratory facilities became available. The new unit should do much to meet this demand and so provide the rising generation of surgeons with something comparable to the opportunities available to their opposite numbers on the other side of the Atlantic.

### RADIOTHERAPY, OXYGEN, AND CANCER

Another interesting development is the establishment at St. Thomas's Hospital, London, of a new unit for the treatment of patients with cancer by means of radiotherapy and high-pressure oxygen. The St. Thomas's workers have already obtained encouraging results from irradiating malignant growths in patients breathing 15 to 20 times the normal anount of oxygen, and they have shown that the convulsions caused by breathing oxygen at such pressures can be prevented by general anæsthesia. The source of irradiation is a cobalt unit, consisting of two 2000-curie cobalt-60 teletherapy heads mounted opposite each other. In front of this is the pressure chamber mounted on rails, which can be positioned between the two teletherapy heads. A comprehensive monitoring apparatus includes an electrocardiograph, a microphone to follow the respiration, a pneumotachograph to measure the tidal volume and minute volume of the respiratory gases, a plethysmograph to indicate limb blood-flows, a electroencephalograph to indicate the depth of anæsthesia, and a polarograph to measure tissue-oxygen tension.

### CORNEO-PLASTIC CONFERENCE

A new departure from the usual pattern of ophthalmological conferences was held in June at the Corneo-Plastic Unit of the Queen Victoria Hospital, East Grinstead—the hospital that achieved such fame during the last War for the outstanding services it rendered to the mutilated survivors of the Battle of Britain. The Corneo-Plastic Unit was set up to carry into civilian life the lessons that had been learned from the combined work of the plastic surgeons and the ophthalmic surgeons during the War. Its threefold purpose is to study eye problems based on the principles of ophthalmic and plastic surgery, to train young ophthalmic surgeons in this field, and to maintain a regional eye bank. During the first ten years of its existence ophthalmic surgeons from over 40 different countries have visited the unit. The scope of the program, and the calibre of the participants in the conference organized by the unit last month, provided ample evidence of the good work achieved by the unit and the high reputation it has achieved at home and abroad. Apart from workers in this country, the participants included Dr. R. Townley Paton of New York, Dr. Joaquin Barraquer of Barcelona, Professor Derrick Vail of Chicago, and Professor Marc Amsler of Zurich.

Canad. M. A. J.
Aug. 1, 1959, vol. 81

### HAZARDS OF BOXING

*The Lancet* has hit the headlines with an outspoken denunciation of boxing. "Time and again," its first leader thundered the other week, "the public has been told that the path of boxing can lead to brain injury, imbecility, blindness, or death . . . The medical case against boxing is now so strong that as doctors we have a clear duty to fight for its total abolition." Doctors, however, have been quick to spring to the defence of the "noble art", three major arguments having been advanced against the prohibitionist plea. The first is that *The Lancet* case is based largely upon American statistics, which are not applicable to this country. The second is that no one is compelled to take up boxing as a career. The third, and most convincing, is that no differentiation is made between amateur and professional boxing. Whatever abuses may result from the commercial exploitation of the latter do not apply to amateur boxing—particularly as practised in schools and boys' clubs. WILLIAM A. R. THOMSON

London, July 1959.

---

# OBITUARIES

DR. W. D. BRACE, 79, died in Saskatchewan on June 3. An Englishman by birth, from Dorking, Surrey, he came to Canada as a child, and graduated in medicine in Toronto in 1910. During the First World War he served overseas with the medical corps. In World War II he again joined the corps and was stationed in Quebec. For 25 years Dr. Brace practised at Biggar, Sask., and then at Melville, Regina, Delisle and Scott. In 1950 he moved to Saskatoon, where he became medical supervisor of the provincial geriatric centre.

Dr. Brace is survived by his widow, three daughters and one son.

DR. C. H. BROWN, 85, a former chairman of the medical board at the Ottawa Civic Hospital and a member of the surgical staff there for many years, died in the hospital on May 14 after a lengthy illness. He was born in Carleton Place, Ont., and graduated in medicine from McGill University in 1898. For the next two years Dr. Brown interned at the Royal Victoria Hospital, Montreal, before starting a practice in Ottawa in 1900. In 1910 he was appointed to the surgical staff of the County of Carleton General Protestant Hospital and remained there until 1924. He served as staff surgeon at the Ottawa Civic Hospital from 1924 to 1934, when he was appointed as a consulting surgeon—a post which he held until his retirement in 1945. In 1926 he was made a Fellow of the American College of Surgeons. Dr. Brown was also a life member of the Ontario Medical Association.

He is survived by one daughter.

DR. G. E. FLANAGAN, 61, died suddenly at his home in Myerstown, Pa., on May 24. A native of Avonmore, Ont., he was educated at Queen's University, Kingston, and graduated in medicine in 1923. After interning at St. Mary's Hospital, Hamilton, he did postgraduate work in New York. For a short time he practised in Hamburg, Pa., and then moved to Myerstown.

He is survived by his widow and one son.

DR. J. S. McARDLE, 42, was killed in an automobile accident in North Dakota on May 29. A former resident of Winnipeg, Man., he served overseas with the R.C.A.F. for six years in World War II and took part in the Battle of Britain. Dr. McArdle graduated in medicine from the University of Manitoba in 1952 and did postgraduate work in St. Boniface Hospital. In 1953 he moved to Minot, N.D.

DR. ANGUS ALEXANDER MacMILLAN, 44, died in Vancouver, on June 23. Dr. MacMillan was born in Guelph, Ont., and was a graduate of Queen's University, 1941. Following internship at the Ottawa Civic Hospital, Dr. MacMillan served in the R.C.N.(R) from 1942 to 1946. He began his postgraduate training in anæsthesia at the Royal Victoria Hospital, Montreal, and completed his training at the Vancouver General Hospital, receiving his certification from the Royal College of Physicians and Surgeons in 1950.

Dr. MacMillan was a senior partner of Associated Anæsthetic Services, Vancouver; a member of the attending staff of the Vancouver General Hospital and the Vancouver Children's Hospital, and of the teaching staff of the University of British Columbia. He was a member of the Canadian Anæsthetists' Society and the American Society of Anesthesiology.

He is survived by his widow, a daughter and a son.

DR. S. C. SKIPPER, 66, a member of the medical staff at the Ontario Hospital, Woodstock, died in that hospital on May 27. Born in Kingsville, Ont., he had practised on Pelee Island for 20 years. In the First World War Dr. Skipper served as a surgeon in the Navy.

He is survived by his widow and a daughter.

DR. C. K. WHITELOCK, 71, died in the Greater Niagara General Hospital, Niagara Falls, Ont., on June 12. Born in Hamilton, he attended Queen's University, Kingston, where he graduated in medicine in 1914. During World War I Dr. Whitelock served overseas with the Royal Army Medical Corps. After his discharge he practised in Saskatoon and later in Harrowsmith, Ont., moving to Niagara Falls in 1929. At the outbreak of the Second World War, Dr. Whitelock joined the R.C.A.M.C. and served for five years. In 1946 he was appointed Medical Officer of Health of Niagara Falls.

Dr. Whitelock is survived by his widow, one son and three daughters.

### MISS GRACE M. SICKLES

We regret to announce the death on June 29 at Troy, New York, of Miss Grace M. Sickles, Associate Research Scientist in the Division of Laboratories and Research of the New York State Department of Health. Miss Sickles is best known as the discoverer with Dr. Gilbert Dalldorf of the Coxsackie virus in 1947. She identified this virus during a study of epidemics of poliomyelitis in New York State, and the virus was named for the village in which the first two recognized human infections occurred. She had previously carried out studies with Dr. Augustus B. Wadsworth on antisera against pneumococci, meningococci and streptococci, on diphtheria toxin and on antibiotic activity of micro-organisms from soil.

# PROVINCIAL NEWS

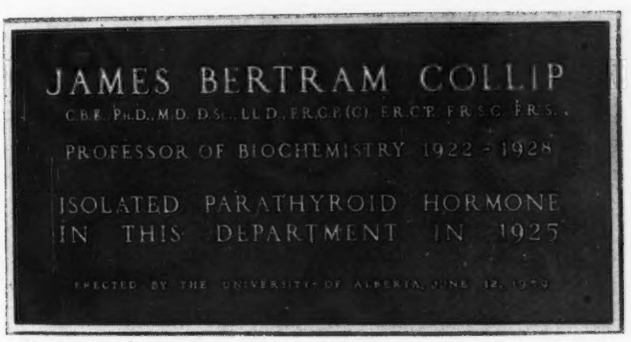
## ALBERTA

As in previous summers two camps for diabetic children are in operation in Alberta. Camp Cadiscasu, at Pine Lake, is operated by the Calgary branch of the Canadian Diabetic Association and the Kinsmen Club of Calgary. It accepts both boys and girls, aged 5-18, up to 40 in number. Camp is held August 16-30 on the B'nai Brith grounds.

In the north the Charles Best Camp is held at the Anglican Church Campsite, Lake Wabamum, August 15-29, with an expected enrolment of 35-40 boys and girls, aged 6-18. The sponsor is the Edmonton branch of the Canadian Diabetic Association. Cost of the operation is $75 per week per child, but the fee is set at $25 per week and this is waived if circumstances warrant.

Both camps are staffed by a medical team as well as program director and counsellors.

On June 12 in Edmonton a bronze tablet was presented to Dr. J. B. Collip, dean of medicine at the University of Western Ontario. The tablet, which was presented by Dr. Walter H. Johns, president of the




**Plaque in the University of Alberta commemorating the discovery of parathyroid hormone.**

University of Alberta, and will be placed in the department of biochemistry there, commemorates Dr. Collip's teaching and research at the university. Dr. Collip was the first to isolate parathyroid hormone, which he did while he was working in the department of biochemistry.

Dr. Percy Sprague, Dr. J. A. L. Gilbert and the Minister of Health for Alberta, Dr. J. Donovan Ross, were recently presented with life memberships in the Canadian Diabetic Association in recognition of their service to the cause of diabetics.

An amendment to the Public Health Act of Alberta prohibits the use of shoe-fitting fluoroscopes in the province.

## SASKATCHEWAN

Fifty-two delegates at the annual meeting of the Saskatoon constituency of the C.C.F. recently called for an immediate reversal of recent policy changes in the provincial government's medical benefits program to old age and disabled persons, charging that the move showed "a declining concern for the humanitarian goals" of the C.C.F. movement.

The conference claimed that the changes from the original policy, whereby recipients of benefits would be responsible for 50% of the cost of drugs and responsible also for physicians' fees beyond an initial 14-day hospital period, were contributing further to the "declining vigour of C.C.F. policies and programs during the last few years".

The resolution, drafted by the association's executive, announced flatly that the executive "is of the opinion that economies in government administration should not be achieved at the expense of this particular section of the population which is least able to fend for itself".

The executive added that since a considerable section of C.C.F. association members in the city "and probably also of the general population" had already experienced "a considerably reduced enthusiasm" for the policies being followed by the C.C.F. government and for what appeared to be "a declining concern for the humanitarian goals of our government", the association was of the opinion that the C.C.F. government could not afford at this time to alienate a still further number of voters.

Planning is under way for a refresher course to be held in Saskatoon in January of 1960, on "Management of injuries of bones and joints".

During June, Dr. C. C. Hopmans spoke at the University Hospital in Saskatoon on "Some aspects of the treatment of osteomyelitis."

Professor Francis E. Stock, professor of surgery and dean of the medical school of the University of Hong Kong, will be visiting Saskatoon August 26 to 29.

Professor Stock is a well-known surgeon, trained in Great Britain, who has written quite extensively in the literature and is particularly interested in some of the rather unusual surgical procedures which occur in China.

G. W. PEACOCK

## MANITOBA

Dr. P. H. T. Thorlakson, President of the Winnipeg General Hospital Medical Alumni Association, has presented a cheque for $1000 to Dr. Henry Guenther, Winnipeg, the first holder of the Fellowship instituted by the Association. He will employ the award for professional advancement.

Dr. James Bennett of the Winnipeg General Hospital radiotherapy department is in Burma to supervise the use of a cobalt therapy unit presented by Canada.

Dr. T. A. Pincock has retired as provincial psychiatrist and has been succeeded by Dr. Edward Johnson, medical director of Selkirk Mental Hospital, who at the present time is making a study of mental hospitals in Europe. Dr. Johnson is president of the Manitoba Medical Association. Dr. Pincock was the first deputy minister of the department of public health and welfare, and was medical director of Brandon Mental Hospital before becoming provincial psychiatrist.

ROSS MITCHELL

Canad. M. A. J.
Aug. 1, 1959, vol. 81

## ONTARIO

Two hundred and sixty-five delegates participated in six sessions of Council meetings receiving and discussing reports during the two-day period preceding the scientific sessions of the Ontario Medical Association in Toronto in May.

The Special Committee on Medical Care and Practice presented an excellent report. While its terms of reference embraced almost the entire field of medicine, the most urgent subject was government intervention in the field of private practice. The committee believes that it would not be in the best interests of all concerned for doctors to participate in an insurance plan administered by government unless the manner of participation is satisfactory to the medical profession.

The beliefs of the committee were summarized thus: (1) Central government has a proper role to play in the health field [this role was outlined in the report]. (2) The people have a right to insure themselves in any manner against possible medical expenses. (3) The demand for a comprehensive government plan is based on dissatisfaction by significant segments of the public with protection afforded by existing plans. (4) Before any plan is formulated by government or its agencies, the medical profession must be consulted to ensure that the plan is realistic in covering the medical needs of the population. (5) The profession should participate in any plan only if the manner of participation is acceptable to it. (6) Participation in any plan must follow the premise that the physician's prime interest is with the patient and the standard of medical care that will be available. (7) If any plan be formulated which is not approved in advance by the medical profession, the doctor should remain outside the plan by making his contract with the patient and not the plan. (8) An effective association is one so united that individual and/or group self-interest is forgotten in the desire to develop and foster policies designed for the common good.

These two recommendations were adopted: "The committee recommends that if government or any body or organization should attempt introduction or legislation or economic sanctions which would interfere with this individual freedom of a patient or a physician, the Ontario Medical Association gives notice that the members of this Associaton will object to the discrimination by refusing to participate in such a plan."

"The committee recommends that the way for each individual in the medical profession to cope with any further extension into the field of private medical practice by government or any other agency is to give heed to the protection of the rights and privileges he now enjoys by not accepting third party payments directly or contracts which interfere with this democratic right of personal liberty and self-determination."

The special committee was requested by Council to investigate the problem of the future of the prepaid medical plans with reference to the implementation of the principles enunciated in the above resolution. It was also asked to determine the views of the profession as to whether or not Physicians' Services Incorporated, Windsor Medical Services, Medical Welfare and Workmen's Compensation Board are within the meaning of third party as used in that resolution.

The committee also presented an opinion on the fee-for-service principle. After outlining its advantages in respect of professional independence and maintenance of the doctor-patient relationship, the opinion ended as follows: "While supporting the fee-for-service principle, we would maintain at all times the individual doctor's right to choose his own method of remuneration. We would, however, ask him to consider before signing a contract whether he is forfeiting his independence, and whether he, his confreres, the members of his section and the profession at large would not be better off under a fee-for-service principle when this is applicable."

Dr. G. D. W. Cameron, deputy minister of health in the federal government, who was head of Canada's delegation to the recent World Health Assembly in Geneva, has been made a Fellow of the Royal College of Physicians of London.

Dr. L. P. MacHaffie, the first medical officer of the Ottawa Public Schools, has retired after 28 years' service in this post. He will be succeeded by Dr. Anna Wilson Sharpe.

Dr. R. G. Warminton, Niagara Falls, has been appointed medical director of the medical products department of Cyanamid of Canada Limited. Dr. Warminton is chairman of the Committee on Occupational Medicine of the C.M.A. and councillor for middle Canada of the Industrial Medical Association.

LILLIAN A. CHASE

Mr. John A. Collins of 70 Cathcart Street, London, Ontario, now in his third year at the University of Western Ontario School of Medicine, London, Ontario, has been awarded a $500 scholarship for research and clinical training this summer in allergic diseases by the Allergy Foundation of America.

Mr. Collins will extend work done by his supervisor, Dr. J. H. Toogood, instructor in medicine, University of Western Ontario, and director, Allergy Laboratory at Victoria Hospital, London, Ontario, on modification of development of the allergic wheal in both humans and experimental animals.

## NOVA SCOTIA

The annual meeting of the Halifax Medical Society was held on April 26 and May 6, with the retiring president, Dr. A. M. Marshall, in the chair. The first session of the meeting was held at the Dalhousie Public Health Clinic. At this meeting, the secretary, Dr. Hereford C. Still, gave a brief report on the Society's activities during the past year. Dr. Still pointed out the poor attendance record of the members of the Society. The records showed that no more than 40% of our members attended the meetings during the year, a very unsatisfactory state of affairs.

At this meeting, Dr. F. Murray Fraser, president of the Board of Directors of Maritime Medical Care, Inc., gave a lengthy report of the operation of Maritime Medical Care, Inc., since its inception ten years ago. He stated that in the first year of the operation of this prepaid medical scheme, the annual budget was but

*(Continued on page 210)*

*(Continued from page 208)*

$37,000. This has grown until today the annual budget is in excess of $2,000,000. During these ten years of operation, Maritime Medical Care, Inc., has suffered a yearly deficit on many occasions. The total of their operations has left them with an overall deficit of some $8000. During the last few years, Maritime Medical Care, Inc., has pro-rated the doctors' accounts at 85%. The prospects of this 85% being increased to 90% are poor indeed. They have adopted the new Nova Scotia schedule of fees, and this goes into operation on July 1. This new schedule of fees is in some respects 25% higher than it was ten years ago. Because of this new schedule of fees, Maritime Medical Care, Inc., have decided to increase their rates to the subscribers. This increase in rates will bring them in alignment with the rates paid by subscribers in similar schemes across Canada. Dr. Fraser stated that during the coming year it was the intention of Maritime Medical Care, Inc., to put 2% of their revenue into a special fund to take care of future contingencies.

The nominating committee brought in the new slate of officers for 1959-60. They are: Dr. John W. Merritt, president; Dr. Donald M. MacRae, vice-president; Dr. Hereford C. Still, secretary, and Dr. Ralph W. M. Ballem, treasurer.

The second portion of this meeting was held at the Nova Scotian Hotel on May 6. This was a mixed affair to which, as has been the custom for the past four years, the wives of the doctors were invited. After dinner, the retiring president, Dr. Marshall, gave an address on the happenings of the past year, both in the local and international fields. After his address, the new president, Dr. John Merritt, was installed in office and addressed us briefly. Dancing was enjoyed until the hour of 1.00 a.m.

Dr. C. G. Harries, coroner of New Glasgow, stated that New Glasgow doctors had refused to perform an autopsy on a highway accident victim because of the municipality's archaic attitude towards paying autopsy fees. A pathologist had refused to perform an autopsy on one Charles Stuart Duggan until reimbursed for a dozen other autopies. Dr. Harries stated that the authorities were asking for professional services at a ridiculous rate of pay. He stated that a fee of $5.00 was provided in the Coroners Act for an autopsy, and another $5.00 if the the doctor testified at the inquest.

Dr. Park, resident pathologist at the Aberdeen Hospital, had submitted bills to the municipality of Pictou County for 12 autopsies. He said he had disregarded the sum set down by law, and asked for the going rate paid by other municipalities. Dr. Harries said the average minimum fee for a complete autopsy with microscopic examination was $40. He stated that he was quite in sympathy with the stand taken by Dr. Park in this matter and hoped a solution would be found in the very near future. In the meantime, Dr. Park has stated that he will not perform any more autopsies until he is paid for the others performed by him, and a satisfactory schedule of fees agreed upon.

Dr. and Mrs. Maynard F. Taylor of Barrington Passage left in June to take up residence in Miami, Florida, where Dr. Taylor will be taking four years of postgraduate work in surgery.

At the recent meeting of the Canadian Tuberculosis Association held in Halifax, Dr. C. J. W. Beckwith, executive secretary of the Medical Society of Nova Scotia, and Dr. Allan R. Morton, commissioner of health of the City of Halifax, were appointed honorary life member of the Canadian Tuberculosis Association.

Dr. H. L. Scammell of Halifax has been appointed chairman of the Medical Committee of the International Association of Industrial Accident Boards and Commission. This is an important appointment which covers the whole of the North American continent.

Dr. E. Garth Vaughan, Halifax, who has been a resident in surgery at the Victoria General Hospital for four years, has received a scholarship for one year's postgraduate study in cancer surgery and research in London, England. This scholarship, awarded by the Canadian Cancer Society, provides for six months' affiliation with Guy's Hospital in London, and a further six months at St. Mark's Hospital.

Dr. Kenneth J. C. MacKinnon, a native of Antigonish, N.S., and a graduate of Dalhousie Medical School, has been appointed urologist-in-chief to the Royal Victoria Hospital, effective July 1, 1959.

Dr. John E. Bethune of Halifax and Berwick has been appointed a National Research Council medical research associate of Dalhousie University. Dr. Bethune is the second recipient of the associateship at Dalhousie, the other being Dr. S. C. Wainwright, associate professor of biochemistry. WALTER K. HOUSE

# FORTHCOMING MEETINGS

## CANADA

WORLD MEDICAL ASSOCIATION, 13th General Assembly, Montreal, Que. (Dr. Louis M. Bauer, World Medical Association, 13 Columbus Circle, New York 19, N.Y.) September 7-12, 1959.

SOCIETY OF OBSTETRICIANS AND GYNÆCOLOGISTS OF CANADA, Annual Meeting, Mont Tremblant Lodge, Mont-Tremblant, Que. (Dr. F. P. McInnis, Secretary, 280 Bloor St. West, Toronto 5, Ont.) September 10-13, 1959.

CANADIAN OPHTHALMOLOGICAL SOCIETY (SOCIÉTÉ CANADIENNE D'OPHTALMOLOGIE), Annual Meeting, Sheraton-Brock Hotel, Niagara Falls, Ont. (Dr. R. G. C. Kelly, Secretary, 90 St. Clair Avenue West, Toronto 7, Ont.) October 6-8, 1959.

CANADIAN OTOLARYNGOLOGICAL SOCIETY (SOCIÉTÉ CANADIENNE D'OTOLARYNGOLOGIE), Annual Meeting, Sheraton-Brock Hotel, Niagara Falls, Ont. (Dr. Donald M. MacRae, Secretary, 324 Spring Garden Road, Halifax, N.S.) October 9 and 10, 1959.

THE CANADIAN SOCIETY FOR THE STUDY OF FERTILITY, Annual Meeting, Queen Elizabeth Hotel, Montreal, Quebec. (Dr. Jean F. Campbell, Secretary-Treasurer, 238 Queen's Ave., London, Ont.) October 23 and 24, 1959.

## CORRECTION

In the list of "General Hospitals in Canada Approved by the Canadian Medical Association for Junior (1st Year) Intern Training", published in the issue of July 1 (81: 51, 1959), the number of teaching public ward beds (medicine) at Hôpital St-Luc, Montreal, is given as 9. The correct number is 94.

Canad. M. A. J.
Aug. 1, 1959, vol. 81

# BOOK REVIEWS

**PATHOGENESIS AND TREATMENT OF PARKINSONISM. Edited by William S. Fields, Baylor University College of Medicine. 372 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $11.75.**

This excellent symposium comes from the Houston Neurological Society, 1958. Papers on pathogenesis and treatment from leaders in the current medico-surgical advances (Ward, Spiegel, Bucy, Schwab, Pool, Cooper, etc.) together with an historical review by Russell Meyers and a summary by Earl Walker compose a valuable picture of reliable American opinion. Modern surgical procedures and matters of local neuro-anatomy and physiology are discussed. As a comprehensive account of the pathogenesis and treatment, it is short on the side of medical neurology and the psychological and social interplay. The older literature, the natural history of the disease, and such important symptoms as slowness, stalling, and poverty of movement, which can operate independently of tremor and rigidity, receive little attention. However, for the "surgical attack" on the problem these papers are an excellent and reliable source of reference presented and published in an admirable form.

**CLINICAL ENDOCRINOLOGY. K. E. Paschkis, A. E. Rakoff and A. Cantarow, Jefferson Medical College, Philadelphia, Pa. 941 pp. Illust. 2nd ed. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, 1958. $18.00.**

This textbook may be considered unusual in that it is not the product of a great many collaborators with a resulting variety of approaches to problems, but rather a book with unity of thought and concept, since the authors work and teach together at Jefferson Medical College and Hospital.

Each endocrine gland is discussed in a systematic fashion under the headings of embryology, anatomy (gross and histological), physiology and pathological physiology, diagnostic procedures and treatment, together with very interesting explanations for the clinical alterations based on a sound understanding of the pathological physiology. Based on this foundation in basic science, the treatment recommended is rational and practical.

Besides the discussions of endocrine glands there are special chapters on obesity, diabetes and infertility. The problems of puberty, adolescence, menstruation, pregnancy and the menopause are all given special consideration. There is as well a very useful chapter on commercial hormone preparations; indeed the practical needs of clinicians are kept paramount throughout the book, and the authors do not bewilder the reader with the many possible methods of treatment but in each case indicate clearly the program of therapy that has proved most valuable in their own experience. This approach to treatment is a conservative "middle of the road" one. Nowhere is this more evident than in their discussion of the place of surgery and radioactive iodine in management of hyperthyroidism.

This book will prove of great value to the medical student, intern and practising physician. There is no better standard-size reference text in endocrinology today, and this book should be available in all hospital libraries.

**INDUSTRIAL HEALTH TECHNOLOGY. Bryan Harvey and Robert Murray. 337 pp. Illust. Butterworth & Co. Limited, London and Toronto, 1958. $9.00.**

This is a comprehensive treatise on the subject of industrial hazards. The causes of industrial disease are outlined, the list including usual chemical causes plus decompression sickness and toxic anæmia. It is also interesting to note that anthrax and glanders are considered among industrial diseases. There is a chapter on high and low barometric pressure including decompression sickness, extremes of temperature, heat cramp, heat exhaustion and heat stroke, while excessive humidity, defective lighting, excessive noise and effects of radiant energy are also covered.

The effects of electric shock and a full description of resuscitation by the Holger-Nielsen method are outlined. Conditions caused by repeated motion and pressure including tenosynovitis, bursitis, occupational cramps and the "white hand" are also outlined. In the experience of the authors, the dead hand or white hand as described here is associated with the use of portable vibrating tools and exposure to vibrations up to 2000 to 7500 beats per minute.

The chapters on organic and inorganic dusts and fumes are interesting. The list of irritants specifically affecting the lungs includes silica, asbestos, bauxite and talc. The authors then discuss the dust and fumes which can cause lung cancer. Miners in Czechoslovakia have a high incidence of lung cancer due to radioactivity of the dusts they inhale in the course of their work; chromates, arsenic and nickel exposures can cause this disease. The book deals briefly with lung tissue irritants and discusses chemicals acting on the central nervous system, the kidneys and liver and the blood. Industrial dermatitis is briefly covered. The principles of prevention of industrial disease include substitution, segregation, enclosure, exhaust ventilation, wet methods, personal protection for the worker, air sampling and control of humidity.

This handbook contains the latest information on industrial disease and allied conditions, and will be most helpful to the industrial doctor and the industrial engineer.

**INTERNATIONALES SYMPOSION UEBER KLINISCHE CYTODIAGNOSTIK. Vom 1-2, März 1957 in Erlangen (International Symposium on Clinical Cytodiagnosis. March 1-2, 1957, at Erlangen). Edited by N. Henning and S. Witte, Erlangen. 216 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1958. $8.10.**

The whole of the International Symposium on Clinical Cytodiagnosis, held in Erlangen, Germany, on March 1 and 2, 1957, is now available in a monograph. It should be noted that the international nature of this symposium was strictly limited, for most of the contributors came either from Germany, Austria or Switzerland. The first topic under discussion was related to general cytology with papers on such subjects as electron microscopical findings in cells, cytochemical findings and experience with the fluorescence microscope. This section was followed by a few papers on microscopical technique, but the major portion of the monograph is concerned with special cytodiagnosis. This contains many interesting papers and discussions on the cytology of a variety of organs and structures. There is a particularly detailed collection of papers on gastro-intestinal cytodiagnosis, as well as a section on the cytology of the bronchi.

*(Continued on page 214)*

*(Continued from page 212)*

**MEDICAL HISTORY OF THE SECOND WORLD WAR. The Royal Air Force Medical Services. Vol. III, Campaigns. Edited by S. C. Rexford-Welch. 730 pp. Illust. Her Majesty's Stationery Office, London, 1958. 105s. net.**

This is the third and last volume in the series dealing with the work of the Medical Branch of the Royal Air Force during the Second World War. It presents a study of the major campaigns in which the Royal Air Force was actively engaged and, as in the previous two volumes dealing with Administration and Commands, it shows how the branch expanded from a small one to an organization whose members served in every quarter of the globe. Although entitled "Campaigns", the emphasis is not so much on describing the course of actions as on surveying critically the efforts made by the medical forces to assist their combatant counterparts in success as well as in adversity.

The story is presented in 11 chapters arranged in chronological order. First, there are the campaigns in France, Norway, Greece and Crete, where the medical services worked against great odds. The second phase includes the Western Desert fighting, where great strides in practical service medicine were made; while the North Russia and West Africa campaigns demonstrate particular medical difficulties in setting up supply bases under two varying climatic conditions. The final phase, covering triumphs in Italy, North West Europe and the Far East, is an excellent demonstration of practical application of knowledge accumulated from the earlier campaigns.

All campaigns recorded usually involved living under field conditions where preventive medicine and elementary health safeguards were of paramount importance. The story told reveals the serious discrepancy which existed between theory and practice in the preparation of units for service in the field. Often, especially during the earlier campaigns, even the minimum standards of hygiene and preventive medicine were neither understood nor observed. This is clearly brought out in the stories told, and frequently resulted in part from a failure of those in authority to appreciate the value of instruction in elementary field hygiene and the refusal to accept or put into practice such training as had been received. An example of this is the story of malaria and dysentery, for which the man-hour losses were formidable, especially when it is remembered that they were in large measure preventable. The editor is to be congratulated for the care which he has taken to record faithfully the difficulties encountered and the mistakes made as well as the sins of omission and of commission.

The story reveals many triumphs but especially it teaches a lesson that an efficiently organized medical service is a vital factor in the success of a campaign.

# PUBLIC HEALTH

SUMMARY OF REPORTED CASES OF NOTIFIABLE DISEASES IN CANADA*
ISSUED BY THE PUBLIC HEALTH SECTION, DOMINION BUREAU OF STATISTICS

| Disease | | Week ended (1959): May 30 | June 6 | June 13 | June 20 | Cumulative total since beginning of year: 1959 | 1958 |
|---|---|---|---|---|---|---|---|
| Brucellosis (Undulant fever) | (044) | 4 | 3 | — | 4 | 47 | 45 |
| Diarrhœa of the newborn, epidemic | (764) | 1 | — | 9 | — | 41 | ‡ |
| Diphtheria | (055) | 1 | 1 | — | 1 | 17 | 28 |
| Dysentery: | | | | | | | |
| (a) Amœbic | (046) | — | — | — | — | 2 | 5 |
| (b) Bacillary | (045) | 19 | 11 | 8 | 13 | 375 | 695 |
| (c) Unspecified | (048) | 1 | 1 | 1 | 1 | 22 | — |
| Encephalitis, infectious | (082.0) | 1 | 1 | 2 | 3 | 17 | 10 |
| Food poisoning: | | | | | | | |
| (a) Staphylococcus intoxication | (049.0) | — | — | — | — | 5 | — |
| (b) Salmonella infections | (042.1) | 1 | 18 | 10 | 13 | 183 | 232 |
| (c) Unspecified | (049.2) | — | — | — | — | 40 | 211 |
| Hepatitis, infectious (including serum hepatitis) | (092, N998.5) | 66 | 62 | 47 | 48 | 2,689 | 1,789 |
| Meningitis, viral or aseptic | (080.2, 082.1) | 2 | — | 2 | 1 | 31 | 3 |
| Meningococcal infections | (057) | 4 | 3 | 7 | 2 | 111 | 145 |
| Pemphigus neonatorum (Impetigo of the newborn) | (766) | — | 1 | — | — | 2 | ‡ |
| Pertussis (Whooping cough) | (056) | 92 | 106 | 104 | 88 | 2,849 | 2,983 |
| Poliomyelitis, paralytic | (080.0, 080.1) | 3 | 1 | 1 | 1 | 29 | 28 |
| Scarlet fever and Streptococcal sore throat | (050, 051) | 482 | 377 | 560 | 532 | 13,962 | 5,669 |
| Tuberculosis: | | | | | | | |
| (a) Pulmonary | (001, 002) | 100 | 91 | 86 | 126 | 2,263 | 2,915 |
| (b) Other and unspecified | (003-019) | 32 | 27 | 37 | 41 | 713 | 944 |
| Typhoid and Paratyphoid fever | (040, 041) | 9 | 15 | 5 | 17 | 394 | 137 |
| Venereal diseases: | | | | | | | |
| (a) Gonorrhœa | (030-035) | 262 | 300 | 233 | 279 | 6,414 | 6,706 |
| (b) Syphilis | (020-029) | 49 | 41 | 64 | 38 | 977 | 965 |
| (c) Other† | (036-039) | — | 1 | — | — | 4 | 2 |

*Excluding Northwest Territories. Figures for the Yukon are received four-weekly and are, therefore, shown in the cumulative totals only.

†Including chancroid, granuloma inguinale and lymphogranuloma venereum.

‡Not reportable.

**WANTED.**—ASSISTANT RESIDENT IN ANÆSTHESIA at Sunnybrook Hospital for one year beginning January 1, 1960. Salary $2700 per annum. Also Senior Intern in Anæsthesia immediately for one year. Salary $2100. Please address all letters of inquiry to Chief Anæsthetist, Sunnybrook Hospital, Toronto 12, Ontario.

**WANTED.**—For St. Thomas-Elgin General Hospital, St. Thomas, Ontario, resident junior rotating intern. Salary $175 per month less $25 per month for full maintenance and laundry. This hospital was opened in May 1954, has 365 beds and is fully accredited. Apply: Superintendent.

**ACTIVE, ACCREDITED,** 160-bed hospital in Montreal, requires resident. Beginning salary $250 per month. Reply to Box 382, CMA Journal, 150 St. George St., Toronto 5, Ont.

**VACANCIES EXIST IMMEDIATELY** for Junior Rotating Interns in an 806-bed general hospital, all services very active. Salary, $125 per month plus full maintenance, with bonus of $25 per month for satisfactory completion of contract. Applications to Dr. A. C. Pickles, Medical Director, Regina General Hospital, Regina, Saskatchewan.

**RESIDENT IN PATHOLOGY FOR TEACHING HOSPITAL.**—IMMEDIATE VACANCY FOR APPLICANT WITH AT LEAST ONE YEAR JUNIOR TRAINING IN PATHOLOGY. GOOD SALARY. APPLY GIVING CURRICULUM VITAE AND NAMES OF THREE REFERENCES TO Dr. Douglas Waugh, Pathologist, Hotel Dieu Hospital, Kingston, Ontario, Canada.

## Practices

**NOTE:** To avoid the publication of misleading information, all advertisers under the classification "Practices" in the Canadian Medical Association Journal should furnish the following information:

Population of community and surrounding territory served.

Number of doctors now practising in the community.

Location of nearest doctor if the community has no resident physician.

Location of nearest hospital.

Description and suggested price of premises for office and residence.

Whether or not an introduction of at least two months' duration may be afforded a prospective purchaser.

**EXCELLENT UNOPPOSED GENERAL PRACTICE** in attractive eastern Ontario village of 1000 population, serving large area. One active doctor within 10 miles; two open hospitals 12 miles away. Large, brick house, fully equipped office, large, well-kept garden. Annual gross over $25,000, includes government salary of $2400. Easy terms, below annual gross, includes salaried introduction of up to two months. Owner specializing. Reply to Box 928, CMA Journal, 150 St. George St., Toronto 5, Ont.

**FOR SALE.**—PHYSICIAN'S LARGE BRICK HOME with contained office located in central Ontario village of 670 with extensive surrounding area. New well-equipped hospital 12 miles. No charge for included active practice. Reply to Box 364, CMA Journal, 150 St. George St., Toronto 5, Ont.

**GENERAL PRACTICE AND LARGE ATTACHED BRICK HOUSE FOR SALE** in central Ontario town. General office equipment included plus full introductions to patients. Reply to Box 361, CMA Journal, 150 St. George St., Toronto 5, Ont.

**GENERAL PRACTICE, MANITOBA.**—Town of 1000, centre of population of about 6000. One other doctor. Modern well-equipped hospital. Annual net income $15,000. Price $15,000 including fully modern house and office equipment. Terms can be arranged. Owner retiring. Reply to Box 362, CMA Journal, 150 St. George St., Toronto 5, Ont.

**UNIQUE OPPORTUNITY** to acquire unopposed old-established ear, nose and throat practice in prairie city. Open hospitals. For details write giving information re age, experience, marital status and religion to Box 363, CMA Journal, 150 St. George St., Toronto 5, Ont.

**SASKATCHEWAN.**—UNOPPOSED PRACTICE serving population of 2000. Nearest doctor 10 miles. Two modern hospitals, one 10 miles, 12 beds; other 20 miles, 30 beds. Combined office and living quarters available for rent. Price including equipment and furniture $4500 on terms. Reply to Box 381, CMA Journal, 150 St. George St., Toronto 5, Ont.

## Fellowships

**FELLOWSHIP IN CARDIOVASCULAR AND THORACIC SURGERY,** available July 1, 1959, at the University Hospital, Edmonton. $3000.00 yearly. Apply—Department of Cardiovascular Surgery, University Hospital, Edmonton, Alberta.

**FELLOWSHIP IN CHILD PSYCHIATRY.** Applications are being considered for training in Child Psychiatry. American Association of Psychiatric Clinics for Children approved training clinic providing both out-patient and resident treatment services. Fellowships provide two-year training program with academic seminars and personal supervision to candidates who have completed two years of approved residency in general psychiatry. Apply to Dr. J. Franklin Robinson, Director, Children's Service Center of Wyoming Valley, Inc., 335 South Franklin Street, Wilks-Barre, Penna.

# MEDICAL DIRECTOR

Smith Kline & French requires well qualified full time physician to give overall direction to its expanding clinical and development organization in Canada.

- Candidates should have university connection and background in either pharmacology, physiology or biochemistry as well as clinical research.
- Should be prepared to accept administrative responsibilities as well as travel.
- Will be required to maintain direct liaison with SKF research and development centers in other countries.

*Interested physicians should write to:—*

**General Manager,**
**Smith Kline & French Inter-American Corporation,**
**300 Laurentian Boulevard,**
**Montreal 9, Quebec.**

# REGIONAL MEDICAL HEALTH OFFICERS

**required by**

# SASK. DEPT. OF PUBLIC HEALTH

**SALARY RANGE:** $796 – $968 per month.

**REQUIREMENTS:** Graduation from an approved school of medicine, diploma or Master's degree in public health and some medical and administrative experience; to do professional, medical and administrative work as medical health officers in organized health regions with populations of approximately 50,000 and to develop regional preventive services and a general public health program.

**BENEFITS:** Three weeks' holiday, three weeks' accumulative sick leave allowance annually with pay, excellent pension and group life insurance plans, opportunity for assisted post-graduate training and other benefits.

**APPLICATIONS:** Forms and further information available at Public Service Commission, Legislative Bldg., and Dept. of Public Health, Health and Welfare Bldg., Regina, Sask., Canada. Inquiries concerning this competition should refer to file No. 6009.

# MEDICAL NEWS *in brief*

*(Continued from page 199)*

## COLOUR IN THE HOSPITAL

In a Berlin hospital, Paschke has been having fun with experiments in colour. Describing his studies of the effects of different colour combinations on the patients and the staff *(Deutsche Gesundheitswesen,* 14: 682, 1959) he points out that he is concerned with three particular parts of the building: (1) the main lobbies, (2) the lobbies and diagnostic and treatment rooms on the wards, (3) the patients' rooms. For the main lobby, he is particularly enthusiastic about a mixture of a medium blue ceiling and medium yellow walls toning off in the lower parts of the walls to a yellow-green and accompanied by a reddish-brown linoleum. Paschke considers that large lobbies require very strong colour contrasts to deprive them of their empty and depressing characters. However, lobbies on the wards cannot be treated so roughly; they require a treatment rather similar to that of the patients' rooms. Here Paschke makes a distinction between the sexes. The male wards have a medium yellow ceiling and bright grey walls. This has a somewhat harsher effect than the combination of a light green wall and a medium yellow ceiling in the women's wards. The floors are laid with green linoleum. This combination of colours gives a pleasing effect of lightness even on rainy days and harmonizes well with any trees in the vicinity. Arched ceilings give the lobbies an "optimistic" air.

The author has also experimented with varieties of colours in patients' rooms, and encouraged free criticism of these combinations. In some cases, three different colours to a room have been chosen with good effect, such as a medium yellow ceiling, two medium grey-blue walls containing door and window, and the remaining walls a strong beige. The author warns us that children respond very differently to colours, and that pædiatric wards therefore need different colour treatment.

## AMERICAN GOITER ASSOCIATION

The American Goiter Association again offers the Van Meter Prize Award of $300 to the essayist submitting the best manuscript of original and unpublished work concerning "goiter—especially its basic cause". The studies so submitted may relate to any aspect of the thyroid gland in all of its functions in health and disease. The award will be made at the Fourth International Goiter Conference in London, England, July 5-9, 1960, where a place on the program will be reserved for the winning essayist if he can attend the meeting. For 1960, the recipient of the award will receive consideration for an award of a travel honorarium.

The competing essays may cover either clinical or research investigations, should not exceed 3000 words in length and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary,

Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, New York, not later than January 1, 1960.

## POSTGRADUATE COURSE IN OCCUPATIONAL SKIN PROBLEMS

The Institute of Industrial Health of the University of Cincinnati announces that the fourth biennial course of instruction in *Occupational Skin Problems* will be given during the week of October 26-30, 1959, by the department of preventive medicine and industrial health, University of Cincinnati, in collaboration with the occupational health program of the United States Public Health Service, and the department of dermatology of the University of Cincinnati.

Physicians interested should write for an application blank to Secretary, Institute of Industrial Health, The Kettering Laboratory, Eden and Bethesda Avenues, Cincinnati 19, Ohio. Early application is advised since attendance will be limited.

## PRECEPTORSHIP PROGRAM AT QUEEN'S UNIVERSITY

The May issue of the *Bulletin of the College of General Practice of Canada* carries a note on the preceptorship program for final-year medical students in the medical school of Queen's University. This program has been arranged in conjunction with the Kingston Chapter of the College of General Practice. Two physicians each take a different final student each week to work with them in the mornings. After lunch the student returns to the hospital and reviews all the cases he has seen on the doctor's rounds, and writes progress notes on them. Students take histories on new patients, perform the physical examinations, outline their suggestions for investigation and treatment and then discuss them with the physician to whom they are assigned. Evening discussions at the practitioner's office on patient records, accounting methods, types of insurance and other matters relevant to general practice are also included. The students are enthusiastic about the system, and private patients have made no complaints. The preceptorship arrangement is described to patients involved. At the end of the term the preceptor submits a report on each of his pupils. The program is additional to a preceptorship program available in the third year at Queen's, in which students spend two weeks in a doctor's home, accompanying him on his rounds.

## LIPID STUDIES IN HEALTH AND DISEASE

At Walter Reed Army Hospital in 1951, a study began, designed to evaluate the reliability of the various methods of lipid determinations in identifying and predicting atherosclerosis. A preliminary report by Mattingly *et al.* (*J.A.M.A.*, 170: 536, 1959) deals chiefly with the results of short-term evaluations and recommendations for future studies. Serum cholesterol and lipoprotein values in 294 normal officers, in 205 patients with myocardial infarction, 101 with angina, 77 with

*(Continued on page 40)*

MEDICAL NEWS *in brief*
*(Continued from page 39)*

arteriosclerosis obliterans, 99 with hypertensive cardiovascular disease, and 100 under observation for cardiovascular lesions were obtained. Whilst the groups could be differentiated on the bases of significant differences in the levels of serum cholesterol and two lipoprotein factions, the variations from person to person within groups were too great to permit identification and prediction of atherosclerosis in individuals.

Of nine officers in whom recognizable vascular disease developed later, none had initial cholesterol values under 250 mg. per 100 c.c. and this measurement was more accurate than the lipoprotein determinations in these subjects in predicting atherosclerosis. Long-term follow-up studies of the remaining normal persons as well as the patients in the various coronary artery, hypertensive and observation groups is expected to furnish more evidence for or against the value of these determinations. As serum cholesterol measurement appears to provide as much information as the more elaborate procedures, serious consideration should be given to its inclusion in periodic health examinations, especially in men under 40 years of age where its elevation when present is most significant.



## MASS RADIOGRAPHY AND CANCER OF THE LUNG

A group of British authors (Posner, McDowell and Cross, *Brit. M. J.*, 1: 1213, 1959) have been collecting information about cases of pulmonary cancer discovered by mass radiography since 1955. They report a follow-up of 238 male cancer cases found by this method in the Birmingham (England) region in the 12 months following July 1955. In the majority of cases the diagnosis was established by objective means, but in one-quarter the course of the disease left no reasonable doubt and two independent sources agreed that cancer of the lung was indeed present. The main point of interest in this study was a comparison of resectability rates between the group referred by general practitioners and those found by mass radiography. However, other information was uncovered which confirmed certain aspects of the disease already published by other authors. Thus it was found that only 6.6% of all the cancer patients were non-smokers, whereas among the general male population they constitute 29.1%. Of the cancer patients 28.3% smoked more than 24 cigarettes per day, whereas 7.1% of the total male population smoked that amount or more daily. Tables compiled for age distribution and according to predominant cell type of tumour show no important difference between general practice cases and the routine survey group.

In all, 223 men with pulmonary cancer were discovered among the general practitioner referrals and 54 cases in the routine survey. The rates were 8.7 per thousand and 0.3 per thousand respectively. Twelve-month survival, irrespective of treatment, was 69 cases (36%) in the first group and 24

cases (50%) in the second. The resectability rate was 30% in the first group and 44% in the second. Of those who underwent resection, 61.4% among the G.P. group and 47.6% of the second group were still alive 12 months after operation. Among the factors affecting resectability, the following are discussed: the importance of age, histological type of cancer, and of diagnostic and therapeutic delays.

Only seven cases of the routine survey group (15%) were classified as truly asymptomatic, while all the general practitioner referrals had symptoms. Of these seven persons three had lobectomies and the fourth had a pneumonectomy. Five of these silent tumours presented with increased hilar shadows or densities close to the pulmonary roots. One patient had a pleural effusion and one a large peripheral ring shadow. Small peripheral coin shadows were not present in any of this group. Although the routine survey cases had a higher resectability rate, the difference between them and the general practitioner cases is not statistically significant.

An addendum to this paper shows that of all the cases irrespective of treatment, 38 G.P. referrals (20%) and 12 routine survey patients (25%) were alive at the end of two years. Of the 57 G.P. cases and 21 routine survey cases of resection, 25 and eight patients respectively were alive two years after operation. The difficulty of early radiological diagnosis of lung cancer is confirmed by the small number of truly "silent" lesions. Men above the age of 35 are found to have the highest incidence of both cancer of the lung and active tuberculosis, and the authors stress the importance and value of concentrating routine surveys on this critical group.

---

## DIABETES, KIMMELSTIEL-WILSON SYNDROME AND NORMAL GLUCOSE TOLERANCE

A 42-year-old man was first treated for diabetes in 1954. At the time he had 2-plus albuminuria and his diabetes responded well to a reducing diet. In 1956, his fasting blood sugar was 201 mg. % and he required insulin only for special situations like treatment of a carbuncle, gangrene of a toe and amputation of the same. Again 4-plus albuminuria and cylindruria were found. In December 1956, he had sciatic neuritis and his urine on this occasion showed no sugar but contained 4-plus albumin and granular casts. His fasting blood sugar was 115 mg. %, blood urea nitrogen 13 mg. % and uric acid 7.5 mg. %. In January 1957 he was found to have marked diabetic retinopathy, moderate hypertension, evidence of left ventricular hypertrophy, and diminution of vibratory sense. Two glucose tolerance tests produced normal curves, and only after stress with cortisone was a slight delay in return of blood sugar to normal levels observed. Renal biopsy showed the characteristic lesions of a diabetic nephropathy as described by Kimmelstiel and Wilson. The authors discuss the inexorable development of diabetic complications of the triad — nephropathy, retinopathy and peripheral neuropathy —as separate from the disorder of insulin function.—W. S. Collens, J. N. Silverstein and G. B. Dobkin: *Ann. Int. Med.*, 50: 1282, 1959.



## DERMATOMYOSITIS AND MALIGNANCY

The association between dermatomyositis and malignancy is discussed by Williams, who summarizes 92 case reports collected from the literature and mentions another 12 case summaries that have appeared since his article was prepared (*Ann. Int. Med.*, 50: 1174, 1959). Williams emphasizes the fact that whilst dermatomyositis is classified as a "collagen disease" it has a significant association with malignancy, present in 15.3% of the published cases of dermatomyositis. He speculates on the possibility that malignancy can start dermatomyositis as a response to local or metastatic disease, and notes the high incidence of breast and ovarian tumours among the reports as a possible indication of endocrine imbalance in these cases. Whatever the relationship between the conditions, it is worth remembering that the presence of dermatomyositis in a patient, especially of middle age, should make one search for possible malignancy.

---

## AMERICAN INSTITUTE OF ULTRASONICS IN MEDICINE

The American Institute of Ultrasonics in Medicine will hold their Annual Meeting on September 2, 1959, at the Leamington Hotel, Minneapolis, Minnesota. The guest speaker at the luncheon meeting will be Russell Meyers, M.D., professor of surgery and chairman, division of neurosurgery, State University of Iowa Hospitals and College of Medicine, who will discuss the potentials of ultrasonics in general surgery and surgical specialties. For further information contact John H. Aldes, M.D., Secretary, 4833 Fountain Avenue, Los Angeles 29, California.

---

## ELECTRONIC ARTIFICIAL LARYNX

The problem of vocal rehabilitation after laryngectomy for cancer is often vexing for patient and surgeon. Most patients can be taught œsophageal voice, an acceptable substitute for normal speech. For various reasons, a few

*(Continued on page 42)*

MEDICAL NEWS *in brief*
*(Continued from page 41)*

cannot learn this technique and may become seriously depressed owing to isolation from their fellows. In recent years, the electronics industry has produced an "artificial larynx" for these unfortunates. Most of these devices consist of a tube about the size of a small flashlight and contain an electrically activated resonator; the instrument is held against the hyoid region and the artificial sound is articulated into words in the normal way. The resulting sounds are generally inferior in quality to those made by accomplished œsophageal speech. The American Bell Telephone Laboratories have very recently developed a new electronic larynx employing three transistors in its circuits; a pitch control is said to result in improved quality of voice. These are welcome developments to those handicapped by laryngectomy.



## FOREIGN MEDICAL GRADUATES

The Annual Report for 1958 of the Educational Council for Foreign Medical Graduates, set up a couple of years ago under the sponsorship of the Association of American Medical Colleges, the American Medical Association, the American Hospital Association and the Federation of State Medical Boards of the United States, describes the rapidly extending work of this new and valuable organization. There is now a large and floating medical population in the United States. In fact, there are now 8600 foreign medical graduates serving in United States hospitals, as against 300 to 400 foreign students in United States undergraduate medical schools. Coming as they do from all parts of the world, these seekers after jobs and opportunities for postgraduate study in the United States have presented a great problem. The Educational Council was set up: (1) to give information to and answer inquiries of foreign medical graduates planning entry to the United States; (2) to evaluate a foreign medical graduate's credentials, his knowledge of medicine and his command of English; (3) to certify those foreign medical graduates who met their requirements which included 18 years of formal education (four at a recognized medical school), a satisfactory knowledge of medicine as measured by the American Medical Qualification Examination, and satisfactory command of English.

In discussing the reasons for the influx of foreign medical graduates into the United States, the Council points to the following factors. The rapidly growing hospitals of the United States have now developed nearly twice as many approved internships as are needed to accommodate the 7000 senior students graduating from U.S. medical schools, the internship stipends in U.S. hospitals have been steadily rising and are now comparable to many fellowship grants, it is now very easy for a foreign medical graduate to obtain permission to do advanced work in medicine in the United States, Fulbright travel funds are often available to such graduates, and the United States is rapidly

*(Continued on page 45)*

MEDICAL NEWS *in brief*

*(Continued from page 42)*

attaining the reputation as a training centre that formerly belonged to such centres as Vienna, London, Paris or Edinburgh.

## ACADEMY OF PSYCHOSOMATIC MEDICINE

The sixth annual meeting of the Academy of Psychosomatic Medicine will be held October 15-17, 1959, at the Sheraton-Cleveland Hotel in Cleveland. This meeting will be oriented and directed to fit the needs of non-psychiatric physicians. Practical everyday office management of psychosomatic problems and emotional disturbances will be dealt with in formal papers, symposia, panel discussions, and small study groups.

The meeting will be open to members of all scientific disciplines, including psychologists, social workers and nurses. Information may be obtained from Dr. Bertram B. Moss, Suite 1035, 55 East Washington Street, Chicago 2, Illinois.

## CANADIAN LIFE INSURANCE FELLOWSHIPS

Financial assistance from the Canadian Life Insurance Medical Fellowship Fund has been granted to 13 medical research workers at 10 medical schools of Canadian universities. The aggregate amount awarded by the Fund this year is in excess of $64,000 and the individual fellowships range in value from $3500 to $6000.

Five of the 13 are for new investigations and the other eight are renewals from previous years. All fellowships are for the period July 1, 1959 to June 30, 1960.

Receiving fellowships this year are the following:

*University of Alberta:* Dr. J. D. Woods for "A study of intercoronary anastomoses in the white races".

*Dalhousie University:* Dr. J. J. Sidorov for the continuation of a research project on obesity.

*Laval University:* Dr. Jean-Marie Loiselle for a continuation of his research on radiation protection.

*University of Manitoba:* Dr. G. R. Cumming for his study on the effect of chlorothiazide in pulmonary hypertension.

*McGill University:* (1) Dr. J. B. Dossetor for a continuation of his study of the mechanism of the diurnal excretion of electrolytes in man; (2) Dr. A. Taussig for his study of mechanisms underlying virus reproduction; (3) Dr. R. F. P. Cronin for a study of pulmonary function and hæmodynamic abnormalities in mitral stenosis.

*University of Montreal*: Dr. M. Lavallée for a study of antiarrhythmic properties of phenothiazine derivatives.

*Queen's University:* Dr. J. W. Kerr for his study of gastrointestinal motility.

*University of Saskatchewan:* Dr. Mitsuko Sada for a study of cardiopulmonary function in patients with emphysema and cor pulmonale.

*University of Toronto:* (1) Dr. A. Rapoport for his studies in connection with hypertension; (2) Dr. Caroline Hetenyi for a study of intestinal malabsorption.

*(Continued on page 46)*

MEDICAL NEWS *in brief*

*(Continued from page 45)*

*University of Western Ontario:* Dr. N. M. Lefcoe for his studies on pulmonary function.

---

## FLUMETHIAZIDE, A NEW DIURETIC

Flumethiazide is a recently developed oral diuretic agent, very similar in structure to chlorothiazide; in fact, the only difference is the replacement of the chloride by a trifluoromethyl group. Rochelle and his colleagues from Houston, Texas *(Antibiot. Med. & Clin. Therapy,* 6: 267, 1959), report studies of its use in 25 cases of hypertensive cardiovascular disease with mild to moderate œdema. It was given in daily doses of 0.5 to 2 mg., and patients had previously received chlorothiazide in exactly the same dose. They found that the drug was approximately of equal potency with chlorothiazide, and was effective in controlling œdema without causing significant serum electrolyte changes. The incidence of adverse reactions was no greater than with the other diuretic (less than 10% of patients observed).

---

## ROOMING-IN

A rooming-in program was instituted at a maternity home in New Zealand in October 1957, following a minor epidemic of staphylococcal skin lesions and breast abscesses. The nursery was abolished, and very little extra equipment was found necessary to introduce rooming-in. The mother was encouraged to care for her infant from the start, and the first 24 hours was used to give supervision and a demonstration of technique in baby care and in cleanliness. Barrier nursing was explained and the danger of hand transfer of infection was discussed. From this time on, nurses had very little to do with feeding or changing the baby. The only visitor allowed was the father.

A questionnaire was mailed to 94 mothers who had participated in this program. Eighty-two (87%) said that they wished to have their future confinements nursed in this way, and only 12 patients were critical of the technique. Those favouring rooming-in felt that both baby and mother benefited from the experience; nine of the 12 who were not in favour of the program said that they got insufficient rest and the other three felt that the strain of responsibility was too great for them. Demand breast feeding was encouraged as the only method compatible with a good night's rest for the mother. The mother learned all the characteristics and reactions of her baby before discharge, and had faced most of the difficult situations while in hospital and overcome them with help and advice of the nurses and the doctor. A plea is made for the wider acceptance on psychological and bacteriological grounds of rooming-in programs. —*New Zealand M. J.,* 58: 163, 1959.

---

## MEDICAL ELECTRONICS

Anyone interested in medical electronics will want to have a copy of the *1958 Canadian Convention Record* which contains the papers on electronics and nucle-

onics presented at the Canadian Convention of the Institute of Radio Engineers in Toronto on October 8, 9 and 10, 1958. The papers reproduced in this volume were given in 24 sessions, two of which were devoted to medical electronics. The medical papers mostly concern descriptions of apparatus devised in Canada for various medical research projects. Thus, Winter and Johnson, of the Defence Research Medical Laboratories, Toronto, describe a simple photo-electric device to record eye movements in response to stimulation of the organ of balance in the head, while Basmajian of the Deparment of Anatomy, Queen's University, discusses his approach to the problem of picking up, amplifying and controlling the minute potentials from normal muscles and feeding the modified potentials as a stimulus to paralyzed or weak muscles. He feels that out of the lessons learned from the normal control of muscular contractions and the increasing technological advances in electronics, there will inevitably come useful apparatus for crippled persons. Ross and Davis of the Allan Memorial Institute of Psychiatry describe stable band pass filters for electroencephalography, and Paul of the Department of Pathological Chemistry, University of Toronto, describes an instrument devised to measure photocell stability.

The papers given at the second session mostly concerned cardiography. Sekelj of McGill University describes electrocardiograph and heart-rate monitor units designed to display simultaneously the ECG and the heart-rate value, while Dower and his colleagues from the University of British Columbia have worked on a zero reference of potential for unipolar leads. Martin of the Queen Mary Veterans Hospital, Montreal, discusses the renewed interest in recent years in the spatial vectorcardiogram. Dower and his colleagues describe a new computer for three-dimensional electrocardiography, and Edinburg of Worcester, Mass., describes several applications of digital analysis in medicine.

Copies of this Convention Record are available at the cost of $5.00 from the I.R.E. Canadian Convention Office, 1819 Yonge Street, Toronto 7, Ontario.

---

## AEROSPACE MEDICINE

The new specialty of space medicine took another step forward recently at the 30th Annual Meeting of the Aero Medical Association in Los Angeles. This organization now has 2000 members and at its meeting it changed its name to that of the Aerospace Medical Association and the name of its journal from *The Journal of Aviation Medicine* to *Aerospace Medicine*.

---

## A CODE FOR DRUG PROMOTION

The Association of British Pharmaceutical Industry has undertaken a commendable action in drawing up a marketing code for drugs which it defines as medical specialties. These are the

*(Continued on page 48)*

MEDICAL NEWS *in brief*

*(Continued from page 47)*

products which are not advertised to the lay public and whose sales therefore depend entirely upon information issued to the medical profession. The new code provides that promotion of these drugs should be based on two principles: (1) that the accuracy and completeness of the information are of paramount importance; (2) that promotion methods should be appropriate to the learning and professional status of those to whom they are directed.

The code requires promotion to include a complete and balanced picture of the new product, including its side effects and contraindications, and distinguishing between what has been proved clinically and pharmacologically and what is merely surmised. Disparagement of competitive products is forbidden and it is suggested that pharmaceutical firms should restrain the mailing of promotional literature to a reasonable amount.

The code contains information on the difficult problem of gifts and hospitality. It is suggested that gifts to pharmacists and doctors should be "of little monetary value" and that any hospitality and entertainment dispensed should be moderate. Finally, to put teeth into the code, it is suggested that firms who offend against it may be deprived of their membership in the Association of British Pharmaceutical Industry.

---

## RELATION OF REACTIONS TO TYPE OF IMMUNIZING AGENT AND ROUTE OF IMMUNIZATION

In Utrecht, Holland (*Nederl. tijdschr. geneesk.*, 103: 1049, 1959), a study was undertaken of the relationship between the type of immunizing agent and the method of immunization on the one hand, and the incidence of reactions after immunization against whooping cough, diphtheria and tetanus on the other. A series of 432 children were given 620 immunizations; 275 received a single injection, 126 two injections and 31 three. Intervals between immunizations were one month. The doses were given either intramuscularly or subcutaneously and results studied one day, three days, eight days, one month and two months after immunization.

More reactions of longer duration were seen after subcutaneous injection than after intramuscular injection, and the type of agent used also affected the incidence of reaction. Multiple antigens caused considerably more reactions, whatever the route of injection, than those without the pertussis component. Sex had no effect, but older children in general had a slightly stronger tendency to react. Reactions were somewhat more severe after a second injection, except when both injections were intramuscular.

---

## THE PYLORIC SYNDROME

Ulcers of the pyloric channel have been known by various other names such as ulcer of the pyloric

ring, pyloric canal ulcer, juxtapyloric ulcer, and ulcer at or near the pylorus. The main symptoms associated with this ulcer are pain, nausea, vomiting, and weight loss. Texter *et al.* (*Gastroenterology*, 36: 573, 1959) report their observations on 67 patients with pyloric channel ulcer whose diagnosis was confirmed at x-ray examination or at operation. The pain is usually or frequently atypical, often colicky in nature, and unrelieved by eating. One-third of the patients complained of pain immediately after eating. Seventy-nine per cent of the patients had nausea and vomiting either almost immediately after eating or as late as two hours after a meal. Weight loss appeared to be due to pain as well as to nausea and vomiting. Significant gastric retention on x-ray examination was frequent and pyloric stenosis was not uncommon. Bleeding occurred in comparatively few, and only one instance of perforation has been reported in the literature. The clinical course is much more accelerated than in ordinary gastric or duodenal ulcers and most patients are hospitalized on at least one occasion. Medical treatment is not very satisfactory and operation was performed on 30 of the 67 patients in this series. Malignancy has been said to be very low in this ulcer and was not found in any of the patients in the present series.



## PRIMARY AND SECONDARY GASTRIC CARCINOMA IN YOUNG ADULTS

Twenty-six cases of gastric neoplasm in adults under the age of 40 have been recorded at St. Bartholomew's Hospital, London, Eng., over the past 10 years. Five of the cases, reported by Thomas (*Gastroenterology*, 36: 582, 1959) in some detail, illustrate the difficulty of diagnosis. Reluctance to consider the diagnosis of cancer of the stomach in young adults is emphasized and it is pointed out as the main reason for the delay between the onset of symptoms and eventual diagnosis. As in other reports, this series showed that some 18% of patients had negative findings on the first barium meal examination. Only three of the patients underwent gastroscopy and in each of these the lesion was visualized. The combination of x-ray examination with gastroscopy to improve diagnostic accuracy is stressed, and reports are quoted which show the high accuracy achieved by this combination of diagnostic procedures. In five patients a gastric ulcer was diagnosed on initial examination; only later was the growth found to be carcinoma. A plea is made for earlier diagnosis of carcinoma of the stomach in young adults and for operation when a simple gastric ulcer fails to respond to medical treatment.

## CONGESTIVE ATELECTASIS: A FATAL POSTOPERATIVE COMPLICATION

Hatch and Carrera (*J. Thoracic Surg.*, 37: 257, 1959) describe the condition designated by them and others as "congestive atelectasis",

*(Continued on page 50)*

MEDICAL NEWS *in brief*
*(continued from page 49)*

which is a complication of the too rapid parenteral administration of fluid. The clinical picture presented by patients with this complication is that of sudden onset of severe dyspnœa, deep cyanosis, fever, laboured expiratory breathing, tachypnœa, tachycardia and hypotension, all aggravated by the infusion of fluid. There are no pathognomonic roentgenographic signs. The condition is characteristically resistant to all forms of therapy directed towards pulmonocardiac failure.

At autopsy in congestive atelectasis, the lungs are heavy and macroscopically the condition suggests gross hæmorrhage. The areas affected are sharply limited; they are liver-like, uniform and dark red. Microscopically, intense capillary congestion, intra-alveolar hæmorrhage, minimal pulmonary œdema, and incomplete expansion of pulmonary tissue are seen.

The onset of congestive atelectasis is sudden. The dyspnœa is severe and clinically indicative of an expiratory obstructive type of breathing. The cyanosis is deep and resistant to all forms of therapy. The physical signs are those usually found in patients with acute left ventricular failure. This is not true in all cases, however.

This complication should not be confused with obstructive collapse of pulmonary tissue. For example, in obstructive atelectasis the cyanosis is light, while it is deep in the congestive form. In obstructive atelectasis the response to oxygen is good, while it is poor in the congestive form. Mediastinal shift is present in the obstructive form, absent in the congestive type. Bronchoscopy is helpful in obstructive atelectasis, not so in the congestive form. The best treatment for this fatal syndrome is, of course, preventive. In all patients in whom hypotension develops postoperatively, it is imperative to determine the cause and treat it physiologically rather than to rely on infusion of fluids to raise the blood pressure to an accepted clinical level. It goes without saying, also, that injudicious parenteral fluid therapy given at dangerous rates of speed should be avoided.



## SCHOLARSHIPS FOR NEUROMUSCULAR DISEASE RESEARCH

The Sister Elizabeth Kenny Foundation announces continuation of its program of post-doctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of the neuromuscular diseases.

The Kenny Foundation Scholars will be appointed annually. Each grant will provide a stipend for a five-year period at the rate of $5000 to $7000 a year depending upon the scholar's qualifications. Candidates from medical schools in the United States and Canada are eligible.

Inquiries regarding details of the program should be addressed to: Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, Inc., 2400 Foshay Tower, Mineapolis 2, Minn.